The Spectrum of Subclinical Best Vitelliform Macular Dystrophy in Subjects with Mutations in BEST1 Gene

Giuseppe Querques,1 Jennyfer Zerbib,1,2 Rossana Santacroce,3 Maurizio Margaglione,3 Nathalie Delphin,2 Lea Querques,1 Jean-Michel Rozet,2 Josseline Kaplan,2 and Eric H. Souto1,4

PURPOSE. To describe the morphologic and functional characteristics of subclinical Best vitelliform macular dystrophy (VMD) in subjects with mutation in the BEST1 gene.

METHODS. Best-corrected visual acuity (BCVA), fundus autofluorescence (FAF), spectral-domain optical coherence tomography (SD-OCT), and electro-oculography (EOG) were assessed in 23 consecutive subjects from nine unrelated families with known mutations in the BEST1 gene (eight distinct BEST1 mutations).

RESULTS. Six subjects were identified with BEST1 mutations (three male, three female; aged 8 to 30 years) without clinically detectable (subclinical) Best VMD (absence of both symptoms and fundusoscopic lesions). All six subjects showed normal FAF findings. In these six subjects, we found five distinct mutations in the BEST1 gene (three [six eyes] out of these six subjects with BEST1 gene mutations). In the other three subjects (six eyes) with BEST1 gene mutations, fundus autofluorescence (FAF) and normal OCT findings. In the three other subjects, we found, on SD-OCT, a thinner and more reflective appearance of the layer between the retinal pigment epithelium and the interface of inner segments and outer segments of the photoreceptor. EOG showed a reduced light-peak:dark-trough ratio in 5 of 12 eyes. Changes on SD-OCT were present in the absence of EOG abnormalities (two of six eyes), and vice versa (one of six eyes).

CONCLUSIONS. Subclinical Best VMD (absence of both symptoms and fundusoscopic lesions) in subjects with BEST1 mutation may vary from the absence of any morphologic and functional abnormalities to the presence of specific SD-OCT and EOG changes. (Invest Ophthalmol Vis Sci. 2011;52:4678–4684) DOI: 10.1167/iovs.10-6550)

From the 1Department of Ophthalmology, Hopital Intercommunal de Creteil, University Paris Est Creteil, Creteil, France; 2Department of Genetics, Necker Hospital, University Paris V, Paris, France; 3Department of Genetics, Ospedali Riuniti, University of Foggia, Foggia, Italy; and 4Unite Fonctionnelle de Recherche Clinique, Creteil, France.


Supported by the Centre de Reference Maladie Rare (CIRM) program.

Submitted for publication August 31, 2010; revised October 27, 2010, and January 5 and February 14, 2011; accepted March 6, 2011.

Disclosure: G. Querques, None; J. Zerbib, None; R. Santacroce, None; M. Margaglione, None; N. Delphin, None; L. Querques, None; J.-M. Rozet, None; J. Kaplan, None; E. Souied, None

Corresponding author: Giuseppe Querques, Department of Ophthalmology, University of Paris XII, Centre Hospitalier Intercommunal de Creteil, 40 Avenue de Verdun, 94000 Creteil, France; giuseppe.querques@hotmail.it.

Vitelliform macular dystrophy (VMD) (OMIM 153,700), also called Best disease,1 has an autosomal dominant pattern of inheritance with very variable penetrance and expressivity. BEST1 (chromosome 11q12-q13)2 is the only gene virtually involved in all Best VMD cases. It encodes a 68 kDa protein called bestrophin-1,3 which is localized to the basolateral plasma membrane of the retinal pigment epithelium (RPE) and appears to exhibit properties of Ca2+-activated Cl-channels.4 Nearly all BEST1 mutations causing Best VMD affect single amino acids, at one of 66 different positions in bestrophin-1.

Best VMD is a clinically heterogenous and pleomorphic disease, having a bimodal onset distribution with one maximum peak before puberty and a second following puberty and extending through the fifth decade of life.5–7

The onset of Best VMD is characterized by symptoms of metamorphopsia, blurred vision, and decrease of central vision. At the fundus a well-circumscribed 0.5- to 2-disc-diameter “egg-yolk” lesion within the macula may be observed.8 This represents the vitelliform stage of the disease, the second of five progressive stages that have been defined on the basis of fundus examination. This early stage of the disease may be followed by the pseudohypopyon stage, the vitelliruptive stage, the subclinical form of the disease, or previtelliform stage, representing the first stage and is characterized by absence of symptoms and normal macula or subtle RPE alterations on fundus examination.

An abnormal electro-oculogram (EOG)5–7 with a reduced or nondetectable light-peak/dark-trough ratio (< 1.55), a blockage effect of fluorescein in the choroid,12 and evidence of increased autofluorescence by the yellow vitelliform lesions7 are considered the main diagnostic criteria in the clinical diagnosis of Best VMD.11,12 Several authors have recently highlighted the usefulness of optical coherence tomography (OCT) in the diagnosis of Best VMD to be demonstrated by the vitelliform material that accumulates in the subretinal space and on the outer retinal surface.13–16 However, no data have been published so far on the different functional and morphologic aspects of the subclinical form of the disease (the previtelliform stage).

Our purpose was to analyze the functional and morphologic characteristics in asymptomatic subclinical subjects issuing from Best VMD families carriers of mutations in the BEST1 gene.

METHODS

Nine Best VMD families segregating BEST1 mutations,17 ascertained at the Creteil University Eye Clinic and at the Foggia University Eye Clinic, were included in this study. Informed consent was obtained according to a Paris XII University and a Foggia University Institutional Review Board-approved protocol. This study has been performed in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki.

Copyright 2011 The Association for Research in Vision and Ophthalmology, Inc.
In each family, affected and unaffected relatives who agreed to participate to the study were screened for the BEST1 mutation identified in the BEST VMD proband using direct sequencing as previously described.\(^\text{17}\)

All individuals included in this study underwent a complete ophthalmologic examination, including assessment of best-corrected visual acuity (BCVA) measured at 4 m with standard Early Treatment Diabetic Retinopathy Study charts, fundus biomicroscopy, color photography of the fundus (TRC-50 retinal camera; Topcon, Tokyo, Japan), fundus autofluorescence (FAF) frames (Heidelberg Retina Angiograph II; Heidelberg Engineering, Heidelberg, Germany), and red free and fluorescein angiography frames (Topcon TRC-50; Heidelberg Retina Angiograph II). Recordings of EOG were done according to the International Society for Clinical Electrophysiology of Vision standard. OCT examination was performed with time-domain (TD)-OCT (OCT 3000 Stratus; Humphrey-Zeiss, San Leandro, CA) or spectral domain (SD)-OCT (HD-OCT, OCT 4000 Cirrus, Humphrey-Zeiss; Spectralis SD-OCT, Heidelberg Engineering). All scans were positioned within the macular area and throughout the vitelliform lesions, based on color fundus photography and FAF. Fundus pictures and SD-OCT scans were analyzed and interpreted independently by three retinal specialists (GQ, JZ, and EHS). Disagreement regarding interpretation of the different features was resolved by open adjudication.

The clinical diagnosis of Best VMD (> second stage) was based on the presence, on fundus examination, of one or multiple subfoveal vitelliform lesions in at least one eye and on the evidence of autofluorescence by the yellow vitelliform lesions. The subclinical form of the disease represents the first stage of Best VMD (the previtelliform stage), which is defined by absence of symptoms and normal macula or subtle RPE alterations on fundus examination. In this study, subjects were diagnosed with the subclinical form of the disease if they were asymptomatic and did not show subfoveal lesions or FAF changes.

On EOG, a reduced light-peak:dark-trough ratio \(\leq 1.55\) was considered abnormal (as per our laboratory protocol). Ratios > 1.55 were considered as normal values.

RESULTS

A total of 23 subjects (11 male and 12 female; mean age, 26.9 years; range, 3 to 70 years), from nine unrelated families with

---

**FIGURE 1.** Pedigree of the studied families. Here all subjects with the subclinical form of Best vitelliform macular dystrophy are presented in white because of the absence of symptoms. In our previous analysis\(^\text{17}\) subjects CT03 and CT14 were presented in black because of exploration abnormalities (OCT and EOG).
<table>
<thead>
<tr>
<th>Subjects</th>
<th>Mutation</th>
<th>Position</th>
<th>Missense Effect</th>
<th>Age, Sex</th>
<th>Age of Onset (y)</th>
<th>Lesion Type</th>
<th>BCVA</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>FG01 (Family FG I)</td>
<td>C&gt;T728 heterozygous</td>
<td>Exon 7</td>
<td>A243V</td>
<td>49, M</td>
<td>41</td>
<td>Atrophy</td>
<td>20/125</td>
<td>20/160</td>
</tr>
<tr>
<td>FG02 (Family FG I)</td>
<td>C&gt;T728 heterozygous</td>
<td>Exon 7</td>
<td>A243V</td>
<td>45, F</td>
<td>37</td>
<td>Vitelliruptive</td>
<td>20/25</td>
<td>20/25</td>
</tr>
<tr>
<td>FG03 (Family FG I)</td>
<td>C&gt;T728 heterozygous</td>
<td>Exon 7</td>
<td>A243V</td>
<td>75, M</td>
<td>67</td>
<td>Pseudohypopion</td>
<td>20/50</td>
<td>20/125</td>
</tr>
<tr>
<td>FG04 (Family FG I)</td>
<td>C&gt;T728 heterozygous</td>
<td>Exon 7</td>
<td>A243V</td>
<td>13, F</td>
<td>—</td>
<td>None</td>
<td>20/20</td>
<td>20/20</td>
</tr>
<tr>
<td>FG05 (Family FG I)</td>
<td>C&gt;T728 heterozygous</td>
<td>Exon 7</td>
<td>A243V</td>
<td>17, F</td>
<td>—</td>
<td>None</td>
<td>20/20</td>
<td>20/20</td>
</tr>
<tr>
<td>FG06 (Family FG II)</td>
<td>G&gt;A275 heterozygous</td>
<td>Exon 4</td>
<td>R92H</td>
<td>16, F</td>
<td>11</td>
<td>Fibrosis</td>
<td>20/160</td>
<td>20/160 CNV RLE</td>
</tr>
<tr>
<td>FG07 (Family FG II)</td>
<td>G&gt;A275 heterozygous</td>
<td>Exon 4</td>
<td>R92H</td>
<td>3, M</td>
<td>2</td>
<td>Vitelliform</td>
<td>20/32</td>
<td>20/32</td>
</tr>
<tr>
<td>FG08 (Family FG III)</td>
<td>G&gt;A44 heterozygous</td>
<td>Exon 2</td>
<td>G15D</td>
<td>3, F</td>
<td>2</td>
<td>Vitelliform</td>
<td>20/25</td>
<td>20/25</td>
</tr>
<tr>
<td>FG09 (Family FG III)</td>
<td>G&gt;A44 heterozygous</td>
<td>Exon 2</td>
<td>G15D</td>
<td>30, M</td>
<td>—</td>
<td>None</td>
<td>20/20</td>
<td>20/20</td>
</tr>
<tr>
<td>CT01 (Family CT I)</td>
<td>C&gt;T274 heterozygous</td>
<td>Exon 4</td>
<td>R92C</td>
<td>8, M</td>
<td>8</td>
<td>Fibrosis</td>
<td>20/50</td>
<td>20/40 CNV RLE</td>
</tr>
<tr>
<td>CT02 (Family CT I)</td>
<td>C&gt;T274 heterozygous</td>
<td>Exon 4</td>
<td>R92C</td>
<td>14, M</td>
<td>8</td>
<td>Fibrosis</td>
<td>20/20</td>
<td>20/20</td>
</tr>
<tr>
<td>CT03 (Family CT II)</td>
<td>T&gt;C689 heterozygous</td>
<td>Exon 7</td>
<td>I250T</td>
<td>11, M</td>
<td>10</td>
<td>Pre-vitelliform</td>
<td>20/20</td>
<td>20/20</td>
</tr>
<tr>
<td>CT04 (Family CT II)</td>
<td>T&gt;C689 heterozygous</td>
<td>Exon 7</td>
<td>I250T</td>
<td>42, F</td>
<td>41</td>
<td>Multi focal</td>
<td>20/25</td>
<td>20/25</td>
</tr>
<tr>
<td>CT05 (Family CT II)</td>
<td>T&gt;C689 heterozygous</td>
<td>Exon 7</td>
<td>I250T</td>
<td>9, M</td>
<td>6</td>
<td>Vitelliruptive</td>
<td>20/125</td>
<td>20/125</td>
</tr>
<tr>
<td>CT06 (Family CT III)</td>
<td>C&gt;T272 heterozygous</td>
<td>Exon 4</td>
<td>T91I</td>
<td>44, M</td>
<td>36</td>
<td>Atrophy</td>
<td>20/125</td>
<td>20/40</td>
</tr>
<tr>
<td>CT07 (Family CT III)</td>
<td>C&gt;T272 heterozygous</td>
<td>Exon 4</td>
<td>T91I</td>
<td>19, F</td>
<td>11</td>
<td>Fibrosis</td>
<td>20/200</td>
<td>20/40 CNV RLE</td>
</tr>
<tr>
<td>CT08 (Family CT IV)</td>
<td>A&gt;G10 heterozygous</td>
<td>Exon 2</td>
<td>T4A</td>
<td>27, F</td>
<td>20</td>
<td>Atrophy</td>
<td>20/50</td>
<td>20/25</td>
</tr>
<tr>
<td>CT09 (Family CT IV)</td>
<td>A&gt;G10 heterozygous</td>
<td>Exon 2</td>
<td>T4A</td>
<td>23, F</td>
<td>16</td>
<td>Pseudohypopion</td>
<td>20/32</td>
<td>20/50 CNV LE</td>
</tr>
<tr>
<td>CT10 (Family CT V)</td>
<td>C&gt;T73 heterozygous</td>
<td>Exon 2</td>
<td>T25W</td>
<td>10, F</td>
<td>9</td>
<td>Vitelliruptive</td>
<td>20/20</td>
<td>20/200</td>
</tr>
<tr>
<td>CT11 (Family CT V)</td>
<td>C&gt;T73 heterozygous</td>
<td>Exon 2</td>
<td>T25W</td>
<td>36, F</td>
<td>30</td>
<td>Vitelliruptive</td>
<td>20/63</td>
<td>20/63</td>
</tr>
<tr>
<td>CT12 (Family CT V)</td>
<td>C&gt;T73 heterozygous</td>
<td>Exon 2</td>
<td>T25W</td>
<td>70, M</td>
<td>60</td>
<td>Pseudohypopion</td>
<td>20/50</td>
<td>20/20</td>
</tr>
<tr>
<td>CT13 (Family CT VI)</td>
<td>T&gt;C26 heterozygous</td>
<td>Exon 2</td>
<td>V9A</td>
<td>44, M</td>
<td>7</td>
<td>Atrophy</td>
<td>20/50</td>
<td>20/200</td>
</tr>
<tr>
<td>CT14 (Family CT VI)</td>
<td>T&gt;C26 heterozygous</td>
<td>Exon 2</td>
<td>V9A</td>
<td>12, F</td>
<td>12</td>
<td>Pre-vitelliform</td>
<td>20/20</td>
<td>20/20</td>
</tr>
</tbody>
</table>

BCVA, best corrected visual acuity; CNV, choroidal neovascularization; F, female; LE, left eye; M, male; RE, right eye.
known mutations in the *BEST1* gene and presenting at least one family member affected with Best VMD, were included in this study (Fig. 1; Table 1). Many affected and unaffected relatives of Best VMD patients (for a total of 63 relatives) were excluded from the study because they were not screened for mutations in the *BEST1* gene; of note, only few (12 out of 63 unscreened relatives) were diagnosed with Best VMD (Fig. 1). Two unrelated individuals screened for mutations were also excluded from the study because they did not carry any *BEST1* mutation; they had no clinically detectable Best VMD with normal SD-OCT and EOG findings.

Among the 23 patients harboring a *BEST1* mutation (Table 1), 17 patients presented with either bilateral (15 of 17) or unilateral (2 of 17) clinically detectable Best VMD, while six patients had 20 of 20 BCVA and normal funduscopic and FAF findings (subclinical Best VMD). These six carrier individuals (three male, three female; aged 8 to 30 years) belonged to five families, each of which segregated a different *BEST1* mutation (Table 2).

Three out of the six patients (subject FG04 and subject FG05, family FG I; subject CT03, family CT II) presented with overall normal SD-OCT findings in both eyes (Figs. 2 and 3). EOG light-peak:dark-trough ratios (Arden ratio) were within normal ranges for five of six eyes (from 1.58 to 5.22), and one eye revealed an Arden ratio $\leq 1.55$ (subject FG06, left eye) (Fig. 3).

In the other three carrier subjects (six eyes) (subject CT01 from family CT I; subject CT03 form family CT II; subject CT14 form family CT VI), we found, on SD-OCT, a thicker and more reflective appearance of the layer between the RPE and the interface of inner segments (ISs) and outer segments (OSs) of the photoreceptor (the Verhoeff’s membrane) (Figs. 4 and 5). In all eyes but two (four of six) from a single patient (subject CT03) (Fig. 5), EOG showed a reduced light-peak:dark-trough ratio (Arden ratio) $\leq 1.55$.

Follow-up evaluation was available for all patients but one (subject CT05). After a mean of 18 months (range 12 to 24 months), BCVA and both funduscopic and FAF findings remained unchanged in all eyes. Also, based on OCT findings, we did not find any sign of disease progression.

A summary of main clinical findings and *BEST1* mutations is presented in Table 1. Even with the same mutation, the age of onset and the stage of the disease were highly variable inter- and intrafamilially. In family FG I, two family members (subject CT04 and subject FG05) showed overall normal funduscopic and SD-OCT findings (at the age of 13 and 17 years, respectively), and one family member with the same heterozygous *BEST1* mutation p.A243V (subject FG03) was diagnosed at a very late age (67 years of age). The heterozygous p.R92H in p.G15D mutations accounted for the earliest disease manifestations (at two years of age, subject FG07, family FG II, and subject FG08, family FG III, respectively) or either a later onset (at the age of 11 years, subject FG06, family FG II).
In complete penetrance and expressivity are well-known features in Best VMD disease. The large variability within and between families of the clinical expression of BEST1 mutations ranging, in our series, from severe Best VMD to subclinical disease is consistent with previous reports.\textsuperscript{17–32} Recently, Laccassagne et al.\textsuperscript{28} found not only a considerable intrafamilial phenotypic variability in patients carrying the p.S144G mutation, but even absence of pathologic phenotype in a patient carrying the isolated p.Y5X mutation in the BEST1 gene. Age of onset may also vary greatly among patients with Best VMD\textsuperscript{29}; however, a recent report highlighted how age of onset may be considered a major criterion to distinguish Best VMD from other similar macular dystrophies not strictly related to mutations in the BEST1 gene.\textsuperscript{30} In this context of broad phenotypic variability, even with a single BEST1 mutation, fundus autofluorescence, optical coherence tomography, and EOG are valuable noninvasive techniques for phenotyping and follow-up of Best VMD patients.\textsuperscript{31,32}

In the current series, among BEST1 mutations carriers diagnosed with subclinical Best VMD (n = 6), half presented with and half without morphologic and/or functional alterations on SD-OCT and EOG, respectively. It is interesting to note that patients without EOG and SD-OCT alterations were young subjects (FG04 13 years old, FG05 17 years old, and FG09 30 years old). However, the absence of EOG and SD-OCT alterations in young subjects was not strictly related to the genotype. In fact, all five BEST1 mutations affected amino acid residues of distinct functional regions of bestrophin.

Three out of six BEST1 mutations carriers presented on SD-OCT a bilateral thicker and more reflective appearance of the layer between the RPE and the IS/OS interface (Verhoeff’s membrane). At first sight, this finding could seem in contrast to the normal localization of bestrophin to the basal aspect of the RPE. In fact, one would expect that the vitelliform material would accumulate in the RPE. Indeed, Arnold et al.\textsuperscript{33} in their clinicopathological report found that the predominant finding was a collection of extracellular material beneath the sensory retina and proposed that this material was derived internally from photoreceptor outer segments and externally from the RPE, the latter first undergoing hypertrophy and then disruption and attenuation. Moreover, in contrast to previous studies that demonstrated massive lipofuscin accumulation in the RPE, Mullins et al.\textsuperscript{26} reported one patient in whom the RPE appeared histologically healthy in some regions of the macula that exhibited loss of photoreceptors. Based on immunofluorescence studies, they proposed that the possible mistargeting of bestrophin may result in a harmful alteration of the ionic milieu of the subretinal space and contribute to the type of photoreceptor cell loss observed histologically. Therefore, we hypothesize that the lesions, at the previtelliform stage, lie beneath the sensory retina and consist of mainly photoreceptor debris, possibly as result of faulty phagocytosis by the RPE, mixed with pigment granules liberated as the RPE undergoes disruption. Interestingly, no strict correlation between electrophysiologic alterations and morphologic changes was evidenced. However, EOG was altered in most eyes with SD-OCT alterations (four of six) and in only one eye without morphologic changes (one of six). These data suggest a trend toward an impaired function, as evaluated by EOG (light-peak:dark-trough ratio $\leq 1.55$), in the presence of morphologic changes (thickening of the Verhoeff’s membrane), yet subclinical (normal BCVA and fundus findings). These data also suggest an overall good sensitivity for SD-OCT to detect or exclude the presence of subclinical Best VMD.
Even though our study was not designed to investigate disease progression, we had the opportunity to follow up five of six of the \textit{BEST1} carrier subjects with subclinical \textit{BEST} VMD over a period of 18 months (mean). BCVA, funduscopy, and OCT findings remained unchanged in all eyes on examination. We acknowledge that this follow-up time is short and probably not enough with respect to disease progression. However, considering patient management and counseling, it is meaningful that subclinical form of the disease may not progress at least in a short-time period.

Our study has several limitations. Many relatives (12 affected and 51 unaffected) of Best VMD patients were not screened for the \textit{BEST1} mutation and thus were excluded from the study: This may represent an ascertainment bias of the current analysis. Moreover, in some Best VMD patients we used TD-OCT that is not very suitable to pick up slight changes. However, given that all subclinical \textit{BEST} VMD patients have been investigated by means of SD-OCT, and that TD-OCT has been used only in patients with clinically detectable \textit{BEST} VMD (disease stage 2 to 5), the different resolutions of the two devices (TD-OCT versus SD-OCT) may have not influenced our data. Finally, we considered light-peak:dark-trough ratio > 1.55 as normal EOG, while other authors use > 1.85 as normal, 1.3–1.85 as mildly reduced, and < 1.3 as severely reduced. However, also considering light-peak:dark-trough ratio > 1.85 as normal, some \textit{BEST1} carrier subjects with subclinical \textit{BEST} VMD, with and without thickening of the Verhoeff’s membrane, still presented normal EOG (two of six subjects, 4 of 12 eyes).

A broad phenotypic variability may be observed in association with specific \textit{BEST1} mutations. In dominant heterozygous Best VMD, the variable phenotype is highlighted in the present study as well as in other studies.\textsuperscript{17–32} The high phenotypic variability is not unique to \textit{BEST1}-related disease and may also be seen in other autosomal dominantly inherited retinal diseases, such as those caused by peripherin or RDS mutations.\textsuperscript{34}

Different mutations might cause Best VMD by different mechanisms. Some mutations in the \textit{BEST1} gene may lead to a more severely affected RPE and formation of extramacular vitelliform lesions,\textsuperscript{20,35,36} however, there seems to be no clear pattern relating type of \textit{BEST1} mutation to severity of clinical expression.\textsuperscript{51} Compound heterozygous, biallelic recessive, or homozygous dominant mutations in \textit{BEST1} may confer a particularly severe phenotype, featuring widespread retinal degeneration, in addition to Best VMD.\textsuperscript{31,37,38} Patch-clamp studies showed a reduced channel function, which was restituted after cotransfection with wild-type bestrophin, consistent with a loss of (channel) function mechanism of disease.\textsuperscript{32} However, biological events other than regulation of ion flow in the RPE, such as ceramide accumulation, may be involved in the bestrophin-associated disease process.\textsuperscript{39} Presently unknown genetic and environmental modifying factors may exert their influence on the phenotypic outcome.

The well-known variability of clinical expression of \textit{BEST1} mutations within and between families,\textsuperscript{17–32} together with our findings on the extremely variable expressivity of subclinical Best VMD, are of particular interest in the era of assisted reproduction.\textsuperscript{40} Because prenatal diagnosis is difficult to offer in a disease with a variable expressivity and with known subclinical forms, preimplantation diagnosis is questionable, especially in individuals with subclinical forms, which have a risk to transmit the disease to descendants.

The evidence of specific SD-OCT and EOG changes in 50% of \textit{BEST1} carriers with no manifest \textit{BEST} VMD symptoms or funduscopic lesions may be of help in families in which the mutation cannot be identified (for instance, mutations lying in unscreened \textit{BEST1} regions). These findings may indeed be valuable to detect asymptomatic carriers, and we propose them as a suitable follow-up.

To date, the Human Gene Database (HGMD http://www. hgm.csf.ac.uk/ac/all. php) reports the identification of 123 different \textit{BEST1} mutations, the very large majority of which are missense mutations or small indel that do not alter the reading frame. The nature of these mutations is consistent with the notion that Best disease-causing mutations in bestrophin-1 lead to a loss of Cl\textsuperscript{−} channel function with a dominant negative effect. However, few heterozygous null alleles have been reported,\textsuperscript{41,42} suggesting that, yet infrequent, bestrophin-1 haploinsufficiency may cause the disease. Furthermore, mutations of \textit{BEST1} splicing regulators have been demonstrated to cause dramatic phenotypes, including vitreoretinchoriopathy and nanophthalmos.\textsuperscript{53} These data, along with the very large variability of clinical presentation of Best disease, sometimes within families, suggest that both the nature of mutations and modifying factors may contribute to the phenotypic variability. It would be interesting to assess in future studies the consequence of missense mutations with variable clinical effect on the Cl\textsuperscript{−} channel function to precisely determine which of them are loss-of-function mutations. Moreover, when high-throughput sequencing will become available, it would be of major interest to perform association studies in Bestrophin-1 carrier patients to identify polymorphisms involved in the modulation of the phenotype.

References


