Phenotypic Subtypes of Stargardt Macular Dystrophy–Fundus Flavimaculatus

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**Objective:** To determine if phenotypic subtypes exist in Stargardt macular dystrophy–fundus flavimaculatus (SMD-FFM).

**Methods:** A cross-sectional study of 63 patients with autosomal recessive SMD-FFM was undertaken. The age of onset, duration of symptoms, visual acuity, and clinical features on fundus examination, color fundus photographs, and fundus autofluorescence images were recorded. Electrophysiological tests, including pattern, focal, and full-field electroretinogram (ERG), electro-oculogram, and color-contrast sensitivity measurement, were also performed.

**Results:** Based on electrophysiological attributes (ERG), patients with SMD-FFM could be classified into 3 groups. In group 1, there was severe pattern ERG abnormality with normal scotopic and full-field ERGs. In group 2, there was additional loss of photopic function, and in group 3, there was loss of both photopic and scotopic function. Differences in scotopic or photopic function among groups were not explained on the basis of differences in age of onset or duration of disease.

**Conclusions:** Patients with SMD-FFM can be classified into 3 groups based on the absence or presence of generalized loss of either photopic or photopic and scotopic function. It appears that these 3 groups may represent distinct phenotypic subtypes in SMD-FFM.


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Since the initial descriptions by Stargardt\(^1\) and Francheschetti,\(^2\) there has been controversy in the literature as to whether Stargardt macular dystrophy (SMD) and fundus flavimaculatus (FFM) represent different clinical entities.\(^3-13\) There is currently no agreement on a clinical classification of this macular dystrophy;\(^3-4,7,10\) some authors have favored the concept of a single disorder,\(^5,8,10,12\) and others have tried to separate them based on clinical findings.\(^9,11,13\)

Previously, fundus features have been used in an attempt to subclassify SMD-FFM and to seek phenotype-genotype correlations,\(^3,7,9,11,12,15\) although many have acknowledged that the criteria used were imperfect. It is well recognized that the fundus appearance, such as the presence or absence of macular atrophy and the distribution of flecks, changes over time in these patients.\(^3,6,8,10,13,16\) In addition, it is often difficult to determine objectively the extent and distribution of fundus lesions without fluorescein angiography, fundus photography, or fundus autofluorescence images. Finally, the fundus appearance does not always correlate well with the retinal function.\(^6,7,10\)

In a recent study,\(^17\) we did not find consistent concordance between siblings with respect to age of onset or fundus appearance. However, there appeared to be good concordance with respect to electrophysiological attributes. In some families, there was loss of macular function alone, whereas in others there was additional loss of photopic or photopic and scotopic function. The isolated abnormality of full-field responses driven by cones is now plausible given the recent identification of ABCR in cones.\(^18\)

On this basis, the purpose of the present study was to test the hypothesis that the different phenotypes, based on electrophysiological attributes, represent different stages of progression of the same disorder. This would be supported by finding a strong association between the degree of functional loss and the duration of symptoms. If this could not be demonstrated, it would be likely that the different electrophysiological phenotypes represent distinct subtypes of SMD-FFM. The study also provided the

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Subjects and Methods

Patients with SMD-FFM examined between July 1997 and October 1998 were asked to join this study. The diagnosis of SMD-FFM was based on the presence of white-yellow flecks at the level of the retinal pigment epithelium involving the posterior pole or extending to the midperipheral retina, with or without overt atrophic macular lesions. In all cases, the diagnosis was verified by fundus autofluorescence imaging. A total of 103 patients with recessive SMD-FFM were examined during the period of the study. Only patients who underwent electodiagnostic tests at our institution were included. In no family was there evidence of autosomal dominant inheritance.

Patient demographics (age, race, and sex), age of onset, duration of the disease, best-corrected visual acuity, and fundus appearance on slitlamp biomicroscopy (distribution of flecks and presence or absence of atrophic macular lesion) were recorded. Color fundus photographs, fundus autofluorescence images, and International Society for Clinical Electrophysiology of Vision (ISCEV) standard electrophysiological studies were also undertaken.

The age of onset was defined as the age at which visual loss was first noted. The duration of the disease was defined as the difference between age at the time of the examination and age of onset of symptoms.

Best-corrected visual acuity was measured with Snellen visual acuity charts. Images of fundus autofluorescence were obtained with a confocal scanning laser ophthalmoscope (cSLO; Zeiss, Jena, Germany) using published techniques. The findings of fundus autofluorescence, fundus examination, and color fundus photography were compared.

The term active fleck was used to define flecks that on biomicroscopy appeared to be composed of white-yellow material at the level of the retinal pigment epithelium. Resorbed flecks were defined as small areas of depigmentation at the level of the retinal pigment epithelium. Flecks were designated to be “in the posterior pole” when they were present only within the vascular arcades, with or without few flecks nasal to the optic disc, and “in the midperipheral retina” when they extended beyond that limit.

Results

Sixty-three patients with SMD-FFM were included in the study. There were 34 female patients (54%) and 29 male patients (46%). The median age of onset was 21 years (range, 5-50 years), and the median duration of the disease was 7 years (range, 0-30 years). At presentation, the median age of the patients was 30 years (range, 8-65 years). Sixty patients were white Europeans (95%), 2 patients were black (3%), and 1 patient was Indian (2%).

Patients in SMD-FFM group 1 had normal full-field amplitudes. Patients in SMD-FFM group 2 had normal scotopic rod ERG but reduced 30-Hz and photopic B wave amplitudes. Lastly, patients in SMD-FFM group 3 had ERG abnormalities involving both rod- and cone-driven responses.

Demographics, age of onset, duration of the disease, and findings on clinical examination, fundus autofluorescence, and electrophysiological studies are presented separately for each group.

Group 1

There were 43 patients (68%) in SMD-FFM group 1, 20 were male (46%) and 23 female (53%) (Table 2). The median age of onset was 23 years (range, 5-30 years), and the median duration of the disease was 7 years (range, 0-30 years) (Figure 1). At the time of examination, the median age of the patients was 30 years (range, 8-65 years). Five patients had an age of onset at 10 years or earlier. In 14 patients (32%), visual acuity in the better-seeing eye was 20/40 or better, in 27 patients (63%), it
was 20/50 to 20/200, and in 2 patients (5%), visual acuity was worse than 20/200.

Fundus examination revealed central macular atrophy bilaterally in 26 patients (60%) (Table 3). Twenty-three patients (53%) had flecks confined to the posterior pole, and in 19 patients (44%) flecks extended toward the midperipheral retina, in 3 of whom they extended to the equator (Table 3). One had macular atrophy but no flecks. He was included in the study because his older brother had macular atrophy and flecks. Two had an area of subretinal fibrosis, 1 of whom reported a history of trauma.

Fundus autofluorescence images were obtained in all but 1 patient (98%). In all patients with atrophic macular lesions detected on fundus examination, there was a corresponding moderately well-defined area or multiple foci of low-intensity signal compared with background in fundus autofluorescence images. In 7 patients, evidence of macular atrophy was detected only by cSLO. Active flecks appeared as foci of increased signal on cSLO images, and resorbed flecks were seen as foci of decreased signal compared with background on cSLO images (Figure 2A-B). Active flecks were seen in all but 1 patient, and resorbed flecks were seen in all but 2. In no patient with flecks confined to the posterior pole (n = 23) did fundus autofluorescent images disclose abnormality in the peripheral retina. In 3 patients (7%), a moderately well-defined area of increased autofluorescence

### Table 1. Electrophysiological Data in a Group of 35 Normal Volunteers*

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Scotopic Rod, 0.01 cd · s/m²</th>
<th>Scotopic Maximal, 11.5 cd · s/m²</th>
<th>30-Hz Flicker (Photopic), 3.0 cd · s/m²</th>
<th>Photopic Single Flash, 3.0 cd · s/m²</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>B Wave Lat, ms</td>
<td>B Wave Amp, µV</td>
<td>A Wave Lat, ms</td>
<td>A Wave Amp, µV</td>
</tr>
<tr>
<td>(mean age, 32.5 y)</td>
<td>95.5</td>
<td>294.5</td>
<td>10.5</td>
<td>362.3</td>
</tr>
<tr>
<td></td>
<td>(5.6)</td>
<td>(1.5)</td>
<td>(54.3)</td>
<td>(1.1)</td>
</tr>
<tr>
<td>51-76 y (n = 19)</td>
<td>81-119</td>
<td>85-370</td>
<td>10-16</td>
<td>155-595</td>
</tr>
<tr>
<td>(mean age, 64.0 y)</td>
<td>96.8</td>
<td>176.4</td>
<td>12.9</td>
<td>301.3</td>
</tr>
<tr>
<td></td>
<td>(10.3)</td>
<td>(1.6)</td>
<td>(98.1)</td>
<td>(5.2)</td>
</tr>
</tbody>
</table>
| *cd indicates candela; lat, latency; and amp, amplitude.

### Table 2. Demographics, Age at Onset, and Duration of the Disease in Stargardt Macular Dystrophy–Fundus Flavimaculatus

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients, No. (%)</th>
<th>Sex, F/M</th>
<th>Age at Examination</th>
<th>Age at Onset</th>
<th>Duration of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43 (88)</td>
<td>23/20</td>
<td>30 (3-65)</td>
<td>23 (5-50)</td>
<td>7 (0-30)</td>
</tr>
<tr>
<td>2</td>
<td>9 (14)</td>
<td>5/4</td>
<td>26 (11-42)</td>
<td>18 (6-32)</td>
<td>5 (2-18)</td>
</tr>
<tr>
<td>3</td>
<td>10 (17)</td>
<td>5/5</td>
<td>31 (16-50)</td>
<td>9 (5-42)</td>
<td>19 (7-29)</td>
</tr>
</tbody>
</table>

**Figure 1.** Age at onset (A) and duration of the disease (B) (median and quartiles) in years for Stargardt macular dystrophy–fundus flavimaculatus groups (group 1, normal full-field amplitudes; group 2, normal scotopic rod electoretinogram [ERG] but reduced 30-Hz and photopic B wave amplitudes; group 3, ERG abnormalities involving both rod- and cone-driven responses). The boxes show the median and 25% and 75% confidence interval (lower and upper quartiles). The whiskers extend to what could be considered the 95% confidence interval. Circles represent values outside the 95% confidence interval.
Table 3. Visual Acuity and Clinical Findings on Slitlamp Biomicroscopy and Autofluorescent Images in Stargardt Macular Dystrophy–Fundus Flavimaculatus*

<table>
<thead>
<tr>
<th>Group</th>
<th>Visual Acuity†</th>
<th>Macular Atrophy‡</th>
<th>Midperipheral Atrophy‡</th>
<th>Flecks Confined to Posterior Pole</th>
<th>Flecks Involving Midperiphery</th>
<th>No Flecks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20/24</td>
<td>14 (32)</td>
<td>27 (63)</td>
<td>2 (5)</td>
<td>33 (77)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>20/50-200</td>
<td>2 (22)</td>
<td>5 (67)</td>
<td>1 (11)</td>
<td>8 (89)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>20/200</td>
<td>0</td>
<td>2 (20)</td>
<td>6 (80)</td>
<td>10 (100)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage).
†Visual acuity in the best-seeing eye.
‡Unilaterally or bilaterally.
§Flecks were present in affected sibling.

was observed at the center of the macula, where only mild pallor could be detected biomicroscopically (Figure 2A-B). Color-contrast thresholds were measured in 35 patients (81%). One patient had normal color vision, 2 (6%) had involvement only of protan and deutan axes, and 32 (91%) had additional elevation of the tritan axis. The elevation in the tritan axis tended to be less marked than that on the protan and deutan axes.

All patients tested (n=39, 90%) had abolished or residual PERG and FERG. Six patients with abolished
PERG had a visual acuity of 20/40 or better in the better-seeing eye. Full-field ERG was performed in all patients (n=43), and EOG was performed in 38 patients (88%) and was reduced in 4 patients (10%). Figure 2C shows the electrophysiological findings (PERG and ERG) corresponding to one of the patients from this group.

Increasing duration of disease was associated with lower photopic B wave amplitude (P=.006, \( r =-0.43 \)) but not scotopic rod B wave amplitude (P=.65, \( r =-0.07 \)) or scotopic maximal A (P=.49, \( r =0.11 \)) or B wave (P=.74, \( r =-0.05 \)) amplitudes (Figure 3). When 3 subjects examined at the onset of symptoms were removed from the analysis, the reduction of photopic function became smaller (P=.02, \( r =-0.37 \)). There was no evidence of any association between age of onset and scotopic rod B wave amplitude (P=.15, \( r =-0.23 \)), scotopic maximal A (P=.06, \( r =0.29 \)) or B wave (P=.47, \( r =0.11 \)) amplitude, or photopic (P=.61, \( r =0.08 \)) function.

GROUP 2

Nine patients (14%) were classified as SMD-FFM group 2, 4 were male (44%) and 5 female (55%) (Table 2). The median age of onset was 18 years (range, 6-32 years), and the median duration of the disease was 5 years (range, 2-18 years) (Figure 1). At the time of the examination, the median age of the patients was 26 years (range, 11-42 years). Four had an age of onset at 10 years or earlier.

In 2 patients (22%), visual acuity in the better-seeing eye was 20/40 or better, in 6 (67%), it was 20/50 to 20/200, and in 1, it was less than 20/200 (Table 3).

Fundus examination disclosed central macular atrophy bilaterally in 5 patients (Table 3). In 1 patient, macular atrophy was seen only in the left eye. Two patients had flecks confined to the posterior pole, and in 6 patients, flecks extended toward the midperipheral retina, in 2 of whom flecks extended to the equator (Table 3). One other patient had no flecks detected on biomicroscopic examination, although flecks were seen in cSLO images.

Fundus autofluorescence images were obtained in all but 1 patient (89%). In all patients, with or without macular atrophy detected on slitlamp biomicroscopy, there was either an area with low-intensity signal or multiple foci of decreased autofluorescence compared with background in the cSLO images. In the one in whom no flecks were detected on slitlamp biomicroscopy, autofluorescence images disclosed active and resorbed flecks confined to the posterior pole. All patients had active and resorbed flecks. In 2 patients with flecks confined to the posterior pole, fundus autofluorescent images disclosed no abnormalities in the peripheral retina.

In the 6 patients tested, color-contrast sensitivity demonstrated increased thresholds in all axes, although relative sparing of the tritan axis was observed in 5 patients.

All patients had abolished PERG and FERG, and EOG results were abnormal in 4 of the 7 patients tested. Figure 4 shows cSLO images and electrodiagnostic findings from one of the patients corresponding to this group.

There was little evidence of progressive loss of scotopic (scotopic rod B wave: \( P=.07, r =-0.63 \); scotopic maximal A wave: \( P=.87, r =-0.06 \); scotopic maximal B wave: \( P=.23, r =-0.44 \)) or photopic (\( P=.73, r =-0.14 \)) function with duration of symptoms, although the photopic responses were abnormally low (Figure 5). There was no relation between scotopic function and age of onset (scotopic rod B wave: \( P=.72, r =0.14 \); scotopic maximal A wave: \( P=.39, r =0.33 \); scotopic maximal B wave: \( P=.39, r =0.33 \)), although photopic abnormality was less marked with later onset of symptoms (P=.003, \( r =0.87 \)).
Ten patients were classified as SMD-FFM group 3 (17%), 5 were male and 5 female (Table 2). The median age of onset was 9 years (range, 5-42 years), and the median duration of the disease was 19 years (range, 7-29 years) (Figure 1). At the time of the examination, the median age of the patients was 31 years (range, 16-50 years). Five patients had an age of onset earlier than 10 years. Visual acuity in the better-seeing eye was 20/50 to 20/200 in 2 patients and worse than 20/200 in 8 patients (Table 3).

Fundus examination disclosed central macular atrophy in all cases (Table 3). In all patients, flecks extended into the midperipheral retina. In 1 patient, flecks were present just anterior to the vascular arcades, whereas in 9 they extended to the equator (Table 3). In 1 patient, an area of subretinal fibrosis was detected. No striking narrowing of the retinal vessels or optic nerve pallor was observed.

Fundus autofluorescence images were obtained in all patients. All had an area of low-intensity signal compared with background at the macula. Five patients had active and resorbed flecks, and 5 had resorbed flecks only. In 1 patient with flecks that extended just anterior to the vascular arcades, fundus autofluorescent images disclosed no abnormalities in the peripheral retina beyond that limit. Well-circumscribed areas or patches of decreased autofluorescence compared with background were detected in the midperipheral retina in 6 patients (Figure 6).

A measurable threshold for the tritan axis only was found in 2 of the 4 patients tested. All patients had abolished PERG and FERG, and EOG results were abnormal in 4 of the 5 patients tested. Figure 7 shows...
Despite the small numbers, in group 3 there appeared to be a relation between deterioration in the amplitude of scotopic rod B wave and duration of the disease ($P = .03$, $r = -0.74$), although this could not be demonstrated with respect to scotopic maximal A ($P = .48$, $r = -0.27$) or B wave ($P = .67$, $r = -0.16$) amplitudes or photopic function ($P = .12$, $r = -0.59$) (Figure 8). We found no evidence of any relation between age of onset and scotopic (scotopic B wave: $P = .72$, $r = 0.14$; scotopic maximal A wave: $P = .90$, $r = -0.05$; scotopic maximal B wave: $P = .53$, $r = 0.22$) or photopic ($P = .39$, $r = 0.36$) function.

One patient could not be classified according to the criteria used. This patient had reduced scotopic B wave amplitude and normal photopic B wave amplitude. Maximal B wave amplitude was normal, and 30-Hz flicker amplitude was abnormal.

COMPARISON BETWEEN GROUPS

Univariate analysis showed that there were differences in scotopic function between groups 1 and 3 ($P < .001$) but not between groups 1 and 2 ($P = .48$) and differences in photopic function between groups 1 and 2 ($P < .001$) and groups 1 and 3 ($P < .001$).

To test the possibility that electrophysiological groups represent different stages of the progression of the disease rather than different phenotypic subtypes, differences in duration of disease and age of onset among groups were studied. The influence of these parameters (duration of disease and age of onset) on the classification was assessed.

At the univariate level, duration of disease appeared to have an effect on scotopic ($P < .001$) and photopic ($P = .002$) function. To assess if differences observed among groups in scotopic and photopic function could be explained only by the different duration of disease among groups, a multiple regression analysis was used. When correcting for duration of disease, differences in scotopic and photopic function between groups 1 and 3 ($P < .001$) and photopic function between groups 1 and 2 ($P < .001$) still existed, indicating that differences in retinal function cannot be explained only by differences in duration of disease alone.

In this model, the median age of onset was found to be lower in group 3 ($P = .005$) than group 1, and the length of history was found to be longer in group 3 than in groups 1 and 2 ($P = .001$ and .003, respectively). Age of onset appeared to have an effect only in photopic ($P = .01$) but not scotopic ($P = .50$) function. When correcting for age of onset, differences in photopic function between groups 1 and 2 and groups 1 and 3 were still present ($P < .001$), suggesting that the classification is not explained by different age of onset among groups.

We sought correlation between other attributes of disease with the classification (Table 3). In this series, patients in group 1 tended to have better visual acuity and more restricted distribution of flecks and atrophy, whereas those in group 3 had the worst visual acuity and more widespread flecks. Macular atrophy was universal in group 3. However, there was considerable overlap of these attributes between the groups. The only feature that was exclusively seen in one group was the presence of atrophy peripheral to the vascular arcades as detected with the cSLO in group 3. Figures 2, 4, and 6, and Figure 9 show autofluorescence images in patients from groups 1 through 3 and demonstrate the similarity of fundus phenotype that exists between groups.
Figure 6. Color fundus photograph (A) and fundus autofluorescence image (B) of the left eye of a 31-year-old woman in Stargardt macular dystrophy–fundus flavimaculatus group 3 (electroretinogram abnormalities involving both rod- and cone-driven responses). Large patches with low-intensity signal were detected in the autofluorescence images, whereas only mild pallor was observed on slitlamp biomicroscopy.

Figure 7. Fundus autofluorescence images (A) and electrodiagnostic findings (B) of a 30-year-old man in Stargardt macular dystrophy–fundus flavimaculatus group 3 (electroretinogram abnormalities involving both rod- and cone-driven responses). Areas of low-intensity signal corresponded with atrophy on biomicroscopy and foci of decreased autofluorescence with resorbed flecks (A). There was decreased amplitude of scotopic, photopic, and 30-Hz flicker that was also delayed (B). PERG indicates pattern electroretinogram.
Three patterns of functional loss were recognized in patients with SMD-FFM. Patients in group 1 had severe pattern ERG abnormality with normal scotopic and photopic ERG B wave amplitudes. Patients in group 2 had additional loss of photopic ERG, and those in group 3 had abnormality of both the photopic and scotopic ERG.

The results of this study do not support the concept that these 3 groups represent different stages in the progression of disease. If this were the case, patients in group 1 would have markedly shorter duration of disease than those in group 2, and patients in group 2 would have a shorter duration of disease than those in group 3. In addition, a strong correlation between loss of scotopic or photopic function and duration of symptoms would have been expected in patients in group 1. These were not observed. The fact that differences in scotopic and photopic function among groups were not explained on the basis of differences in duration of disease or age of onset among groups supports the concept that these electrophysiological groups may represent different phenotypic subtypes in SMD-FFM.

Previous studies3,7,9,11,13,14 have addressed the issue of classifying patients with SMD-FFM according to the presence and distribution of fundus lesions. It has been reported by some that patients with lesions confined to the macula tend to have normal ERGs, whereas those with widespread retinal involvement often have peripheral functional abnormalities.6,7,10,13 By contrast, it has been shown that generalized cone or cone and rod involvement can occur in patients with visible manifestation of the disease restricted to the macula and that a normal ERG may be obtained in patients with peripheral retinal changes.6,7,10 Little evidence has been presented that demonstrates correlation of function with the centrifugal extension of morphological changes. Aaberg10 described 3 patients in whom fundus changes initially confined to the macula extended to the peripheral retina. These patients had peripheral cone and rod dysfunction at the initial visit. Armstrong and colleagues13 and Moloney and associates9 found deterioration of retinal function over time in some patients, although it was not specified how this related to preexisting functional abnormalities. One observation that is in conflict with a strict segregation of patients is that of Hadden and Gass,6 who reported 2 cases with apparently normal electrophysiological responses at the initial visit who had an abnormal ERG on follow-up. Although this finding supports the possibility of progression from normal to abnormal peripheral function in some patients, it preceded the introduction of ISCEV standards for electrophysiology, and the existence of previous and undocumented ERG abnormalities in those cases cannot be excluded.

In the present series, it was not possible to predict the pattern of functional loss based on findings of fundus examination. A high percentage of patients in group 1 (Table 3) with functional loss restricted to the macular area had widespread retinal abnormalities similar to those found in groups 2 and 3. The only clinical characteristic that distinguished our groups was the presence of patches of atrophy outside the vascular arcades, which was seen in some but not all patients in group 3 as detected by fundus autofluorescence imaging. This highlights the value of fundus autofluorescence studies in the characterization of patients with SMD-FFM. This novel technique, which can be used to assess the status of the retinal pigment epithelium, and, in an indirect manner of the photoreceptors, allows simultaneous imaging of active flecks and areas with photoreceptor cell loss. In several cases, areas of atrophy and flecks were only detected in cSLO images.

We used PERG to assess functional abnormalities at the macula. Severe PERG abnormalities were present in all patients studied, even when the visual acuity was
still good. In our experience, this is unusual in other inherited macular dystrophies and confirms our previous findings.17

As in other proposed classifications,14,20 we acknowledge that the differences observed among groups might not be absolute and that it is possible that some patients
may change from one group to another. We have used age of onset and duration of the disease to test our hypothesis, and, further, we acknowledge that these parameters are subjective and dependent on the patient's ability to recognize visual symptoms. Only prospective studies over a long period using consistent electrophysiological recordings would provide a definitive answer. However, the results of this study provide no evidence to suggest that SMD-FFM is a single progressive disorder. Functional characteristics in SMD-FFM, as demonstrated by electrophysiological studies, may correlate with the nature of the mutation within the ABCR gene.

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