Intrafamilial Variation of Phenotype in Stargardt Macular Dystrophy–Fundus Flavimaculatus

Noemi Lois,1,4 Graham E. Holder,2 Frederick W. Fitzke,5 Catherine Plant,1 and Alan C. Bird1

PURPOSE. To evaluate the intrafamilial phenotypic variation in Stargardt macular dystrophy–Fundus flavimaculatus (SMD–FFM).

METHODS. Thirty-one siblings from 15 families with SMD–FFM were examined. Age of onset, visual acuity, and clinical features on fundus examination and fundus autofluorescence images, including presence or absence of central and peripheral atrophy and distribution of flecks, were recorded. In addition, electrophysiological studies were undertaken.

RESULTS. Large differences between siblings in age of onset (median, 12 years; range, 5–23 years) were observed in six of the 15 families studied, whereas in 9 families differences in age of onset between siblings were small (median, 1 year; range, 0–3 years). Visual acuity varied two or more lines among siblings in nine families. In 10 families (67%) siblings were found to have different clinical appearance on fundus examination and fundus autofluorescence images, whereas in 5 families (33%), affected siblings had similar clinical features. Electrodagnostic tests were performed on affected members of 12 families and disclosed similar qualitative findings among siblings. In nine families there was loss of central function only; in two, global loss of cone function; and in one, global loss of cone and rod function.

CONCLUSIONS. In this series, although differences in age of onset, visual acuity, and fundus appearance were observed between siblings, electrophysiological studies demonstrated intrafamilial homogeneity in retinal function. The findings are difficult to reconcile with expression studies showing ABCR transcripts in rod photoreceptors but not in cones. (Invest Ophthalmol Vis Sci. 1999;40:2668–2675)

In 1909 Stargardt1 described a recessive inherited macular dystrophy characterized by the presence of an atrophic macular lesion associated with white flecks. There appeared to be a disproportional loss of visual acuity when compared with the fundus appearance early in the course of the disease. Later, Franceschetti2 proposed the term “fundus flavimaculatus” to designate a peculiar fundus affection in which the hallmark was the presence of white-yellow deep retinal flecks, varying in size, shape, opaqueness, and density and limited to the posterior pole or extending to the equatorial region. In some patients the macula was involved in a fashion similar to Stargardt’s disease.3 Despite attempts to devise a clear distinction between the two conditions on the basis of age of onset and loss of function, most researchers now support the view that Stargardt macular dystrophy (SMD) and fundus flavimaculatus (FFM) are not separate entities but that there is variation in severity in this autosomal recessive inherited trait.4–9 In support of this view is the observation that mutations in the ABCR gene may be responsible for all cases of SMD–FFM.10,11

In SMD–FFM there is wide variation in age of onset, clinical appearance, and severity of the disease.7–9,12–14 Furthermore, whereas in some patients the disease appears to be confined to the central retina, in others peripheral involvement ensues giving rise to very poor vision.4–9 This variation could be explained on the basis of different mutations in ABCR or the influence of other genes on the phenotype. Information regarding intrafamilial phenotypic homogeneity or heterogeneity would resolve this issue, but few such studies have been undertaken.4–6,14 Some reports have favored the existence of a similar pattern of involvement and severity of the disease within families.5,6 Others have described the coexistence of different phenotypes in members of the same family.3,9

The present study was designed to evaluate the phenotypic intrafamilial similarity or variation in SMD–FFM.

METHODS

All families with more than one sibling affected with SMD–FFM were included in this study. The diagnosis of SMD–FFM was based on the presence of white-yellow flecks at the level of the retinal pigment epithelium (RPE), with or without atrophic macular lesions. Thirty-one affected individuals from 15 fami-
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RE, right eye; LE, left eye; CCS, color contrast sensitivity; EOG, electro-oculogram; 30 Hz, 30-Hz flicker; A, abnormal; N, normal; N/A, not available; N/R, not reliable.

* Macular atrophy detected in one eye only.
lies were identified. In no family was there evidence of autosomal dominant inheritance.

Patient demographics (age, sex), age of onset, duration of the disease, best corrected visual acuity, and fundus appearance (presence or absence of macular and peripheral atrophy, and distribution of flecks) were recorded. In addition, color fundus photographs and fundus autofluorescence images were obtained, and electrophysiological studies were undertaken.

The age of onset was defined as the age at which decreased visual acuity was first detected. The duration of the disease was calculated as the difference between the age at the examination and the age of onset.

Best corrected visual acuity was measured with Snellen visual acuity charts. Visual acuity was considered to be different between siblings when there was a difference of two or more lines with the better seeing eye.

Areas of atrophy and flecks were recorded by fundus autofluorescence imaging using published techniques. Autofluorescence images were compared with findings on fundus examination and color fundus photographs. Based on the presence or absence and extent of atrophy and presence and distribution of flecks within the retina, siblings were classified as having “similar” or “different” fundus appearance. The disease was considered to be confined to the posterior pole whenever atrophy or flecks were present only within the vascular arcades, with or without a few flecks nasal to the optic disc. The involvement was designated as peripheral whenever atrophy or flecks extended beyond the vascular arcades.

Twenty-two patients from 12 families underwent electrophysiological investigation. Protocols recommended by the International Society for Clinical Electrophysiology of Vision were used.\(^{16,17}\) Color contrast sensitivity, pattern and focal electroretinogram (ERG), full-field ERG (including rod-specific response, bright-white-flash mixed response, 30-Hz flicker response, and the photopic single-flash ERG), and electro-oculogram were performed. Qualitative functional differences between siblings were evaluated.

This study was approved by the ethics committee of Moorfields Eye Hospital and was conducted according to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients.

**RESULTS**

The age of onset, duration of the disease, visual acuity, clinical features, and results of electrodagnostic tests are summarized in Table 1. In all patients there was symmetry of fundus appearance between the two eyes, except in two patients (a woman 42 years old, family 10; a man 33 years old, family 13) in whom asymmetry between eyes was noted (macular atrophy was present in the left eye but not in the right eye).

Large differences between siblings in age of onset (median, 12 years; range, 5–23 years) were observed in 6 of the 15 families studied (families 3, 4, 7, 10, 11, and 12), whereas in 9 families differences in age of onset between siblings were small (median, 1 year; range, 0–3 years). In eight families, the onset of the disease occurred at an earlier age in the younger sibling (families 3, 4, 6, 8, 9, 10, 11, and 13).

Visual acuity was different between siblings in nine families. In 11 families (1, 2, 4, 7, 9, 10, 11, 12, 13, 14, and 15) the sibling with longer duration of the disease and who usually also had an earlier age of onset had the worse visual acuity (Table 1). Ten patients with a median duration of the disease of 2 years (range, 0–15 years) had visual acuity of 6/12 or better in at least one eye. Four of these patients had marked asymmetry in visual acuity between eyes (≥4 lines).

Areas of atrophy at the macula detected by fundus examination appeared as well-defined areas or multiple confluent foci of decreased signal compared with background on autofluorescence images. Those flecks that on biomicroscopy appeared to consist of an accumulation of white-yellow material at the level of the RPE were seen on confocal scanning laser ophthalmoscopic (cSLO) images as areas of increased signal compared with background. By contrast, when flecks appeared biomicroscopically as areas of depigmentation at the level of the RPE, fundus autofluorescence images disclosed focal areas of low-intensity signal compared with background. In some patients, areas of atrophy or flecks not detected biomicroscopically, usually located in the midperipheral retina, were easily recognized on cSLO images. In one patient (girl 8 years old, family 14) with decreased visual acuity but no obvious abnormality on fundus examination, cSLO disclosed focal areas of increased autofluorescence at the fovea.

In 10 families (67%) siblings had different fundus appearance (families 2, 3, 4, 8, 9, 10, 11, 12, 13, and 14; Table 1). In three families, the age at the time of the examination, the age of onset, and the duration of the disease were very similar between siblings (families 8, 9, and 13; Table 1). Figures 1 through 5 show fundus autofluorescence images of five of these sibling pairs (families 3, 4, 8, 12, and 13).

In five families (33%) affected siblings were found to have similar fundus appearance (families 1, 5, 6, 7, and 15; Table 1). In two of these (families 1 and 5), similar age, age of onset, and duration of the disease were observed between siblings (Fig. 6).

Color vision was abnormal in all patients tested (n = 18). In 10 patients, although increased thresholds for all axes were detected, a moderately severe elevation of protan and deutan axes with relative sparing of the tritan axis was observed. Three patients had involvement only of the protan and deutan axes, whereas in five patients, all axes were affected in a similar fashion.

In all patients tested (n = 21), pattern ERG (PERG) and focal ERGs showed very reduced (≤0.5 μV) or abolished responses. Six of these (nine eyes) had visual acuity of 6/12 or better (Table 1). PERG and focal ERG abnormalities did not appear to be related to the distribution of flecks. In addition, there was no close relationship between the PERG amplitudes and the extent of atrophy. Some patients with no atrophy had extinguished PERGs, and others with central atrophy had residual (abnormal) activity.

Full-field ERG was performed in members of 12 families (25 patients). Eighteen patients of nine families (1, 2, 3, 4, 7, 8, 9, 12, and 13) had normal full-field ERGs implying that photoreceptor dysfunction was limited to the macula. Five patients of two families (6 and 10) had abnormal cone-derived responses with normal rod activity. Two siblings (family 5) had abnormal cone and rod ERGs. Electro-oculogram, performed in 23 patients from 11 families, was abnormal in 5 patients.

In all families siblings had similar qualitative electrophysiological abnormalities, although quantitative differences existed. Figure 7 shows scotopic rod-specific response, bright-white-flash mixed response, 30-Hz flicker, photopic single-flash ERG, and PERG of one sibling from families 4, 5, and 10.
DISCUSSION

That differences in phenotype may exist in SMD–FFM is reflected in the few reports in the literature addressing intrafamilial phenotypic variation. Although Hadden and Gass and Noble and Carr found a similar distribution of fundus lesions and severity of involvement in six and five sibling pairs, respectively, intrafamilial differences were detected in four of nine families reported by Armstrong et al. Because these investigators did not provide details of the fundus appearance and functional status of these patients, it is difficult to assess the degree of concordance of phenotype between siblings. Aaberg studied siblings from 14 pedigrees in which an autosomal recessive inheritance was suspected. He found that affected members of the same family of similar ages (i.e., ages separated by 3 years or less) usually had a very similar pheno-

FIGURE 1. Autofluorescence images of a sibling pair (family 3). The younger of the two siblings (top), aged 53 years, had an earlier age of onset and a more widespread involvement than his older sister, aged 59 years (bottom).

FIGURE 2. Autofluorescence images of a sibling pair (family 4). The younger sibling, aged 30 years, had diffuse foci of increased and decreased autofluorescence and an earlier age of onset (top). Her sister, aged 33 years (bottom), had only focal changes.
type, whereas when the difference in age among affected members of a family was more than 3 years, there was no concordance of ophthalmologic and functional findings. In his series, Aaberg noted the intrafamilial coexistence of phenotypes compatible with Stargardt’s disease and fundus flavimaculatus, and thus favored the concept that there was no clear distinction between these two entities.

In the present study differences in age of onset, visual acuity, and fundus features were detected between siblings. A large difference in age of onset between siblings was found in 6 of the 15 families studied. Although the age of onset is subjective, being dependent on the patient’s ability to recognize visual symptoms, it appeared that the difference in age of onset observed in some families was real. Furthermore, in three families the diagnosis was established in the younger sibling first when the older affected sibling was still asymptomatic.

Given that the fundus appearance in patients with SMD–FFM may change throughout the years, differences between siblings in the presence and distribution of fundus features were detected. A wide range of fundus changes were observed in some families. Figure 3 shows an example of this variability, where the younger sibling (top) had a 1-year history of bilateral visual loss and foci of increased and decreased autofluorescence at the posterior pole, while his older brother (bottom) had diffuse areas of increased and decreased autofluorescence throughout the posterior pole.

Figure 4 shows another sibling pair (family 12). The younger sibling, aged 49 years (top), had a 15-year history of decreased visual acuity, foci of increased and decreased autofluorescence at the posterior pole, and vision of 6/60 right eye and 6/12 left eye. Her brother, aged 60 years, symptomatic for 38 years, had large areas of decreased autofluorescence at the posterior pole and vision of 6/60 right eye and 6/36 left eye (bottom).
lesions could represent different stages in the progression of the disease. However, in this series differences in fundus appearance between siblings were detected even when the age, age of onset, and duration of the disease were very similar.

In 12 families in which electrodiagnostic studies were performed, the same qualitative functional abnormalities among siblings were detected whatever the disparity of age, age of onset, duration of the disease, or fundus appearance. It appeared that functional loss was either limited to the macula or generalized with loss of peripheral cone, or cone and rod function and that this was a characteristic of the disease in a single family. It appears that a similar conclusion can be drawn from the data published by Aaberg.4 If this is confirmed, it suggests that electrophysiological tests have a prognostic value—that is, patients with early peripheral cone and rod involvement have a higher risk of development of peripheral visual loss and thus more severe disease.

**FIGURE 5.** Autofluorescence images of a sibling pair (family 13). Both siblings had similar age, age of onset, and duration of the disease. Marked differences between the siblings in extension and distribution of fundus lesions are manifest.

**FIGURE 6.** Autofluorescence images of a sibling pair (family 1). Foci of increased autofluorescence are seen in both siblings, with very similar distribution.
Macular function was evaluated, in the present study, by using PERG and focal ERG. PERGs and focal ERGs were found to be severely reduced or abolished in all patients tested, even when visual acuity was still good. In our experience, this finding is uncommon in other inherited maculopathies. Although further studies in a large group of patients are needed to confirm this finding, it appears possible that abnormalities in PERG and focal ERG could be used to establish an early diagnosis and to differentiate SMD–FFM from other macular dystrophies, especially in early stages of the disease when fundus flecks may not be evident.

Focal increased fundus autofluorescence an index of increased lipofuscin content in the RPE appeared to correspond well with those flecks consisting of white-yellow material at the level of the RPE. Similarly, well-defined areas of increased fundus autofluorescence compared with background were detected, at the macula, in some patients. This corresponds with light and electron microscopic studies, which show abnormal accumulation of intracytoplasmic material in the RPE, identified as lipofuscin, and with a previous study by Delori et al., in which abnormally high levels of fundus autofluorescence were observed in five patients with SMD–FFM. Although the distribution of white flecks and atrophy differed between siblings, this was not considered good evidence of qualitative differences in disease within the sibship. Fundus autofluorescence studies provided additional help in establishing the diagnosis of SMD–FFM, especially in patients with the end stage of the disease in whom resorbed fundus flecks were very difficult to detect or were not visualized on slit lamp biomicroscopy.

Mutations in the ABCR gene, located in the short arm of chromosome 1, have been identified recently in patients with SMD–FFM. Furthermore, it has been hypothesized that different mutations within the ABCR gene would probably account for the wide phenotypic heterogeneity observed in patients with SMD–FFM. However, in an autosomal recessive disorder, siblings could be expected to have the same alleles, such that the variation between siblings could not be caused by different mutations or other sequence changes in the ABCR genes. Differences between siblings may indicate the influence of other “modifying genes.” The differences in phenotype between siblings appear to be quantitative rather than qualitative with respect to the distribution and nature of photoreceptor dysfunction, which may reflect the influence of different mutations in ABCR. The modification of phenotype by other genes relates to the age of onset, distribution of fundus lesions, and speed of progression. Overall, the findings indicate that, when considering the putative influence of a mutation in the ABCR gene on cellular function, the qualitative attributes of
functional loss should be taken into account rather than the age of onset, loss of visual acuity, and fundus features. It would be surprising if the distinction regarding distribution of photoreceptor dysfunction is absolute, because in most cases the disease occurs in the compound heterozygous state.

Finally, expression studies in mouse, rat, bovine, and macaque ocular tissues have demonstrated the presence of ABCR transcripts in rod photoreceptors but not in cones,\(^\text{10,24}\) which is difficult to reconcile with the gene causing macular dystrophy. It is even more difficult to explain the widespread cone involvement with normal rod function in members of two families presented here (6 and 10). It appears unlikely that the degree of cone dysfunction observed in some of these patients could be explained on the basis of a primary lesion within the rod photoreceptors, as has been previously proposed.\(^\text{10}\) Further studies are needed to resolve this dilemma.

References