TABLE 1. Clinical Data and Molecular Genetic Status of 59 Patients With Stargardt Disease (*Continued*)

Pt	Onset (y)	Age (y)		logMAR VA		Variants Identified[a]
		BL	FU	BL	FU	
52	11	31	42	1.3/1.3	2.0/2.0	p.Arg1108His
53	5	32	43	2.0/2.0	2.0/2.0	c.5461-10 T>C / p.Cys2150Tyr
54	5	32	43	2.0/2.0	2.0/2.0	c.5461-10 T>C / p.Cys2150Tyr
55	7	36	47	1.3/1.3	3.0/1.3	c.5461-10 T>C / p.Cys2150Tyr
56	13	39	50	1.25/1.56	3.0/3.0	ND
57	23	42	52	1.56/1.0	1.0/1.0	p.Leu747Cysfs*787
58	40	43	54	0.18/0.18	0.78/0.78	ND
59	23	54	65	0.78/1.0	1.0/1.0	p.Ile156Val

BL = baseline; FU = follow-up; logMAR = logarithm of minimal angle of resolution; ND = not detected; Pt = patient; VA = visual acuity.
[a]Putative novel changes are shown in bold.

TABLE 2. Distribution of Electrophysiologic Groups at Baseline and at Follow-up in Stargardt Disease

Electrophysiologic Group[a] at Baseline[b]	Electrophysiologic Group[a] at Follow-up[b]		
	Group 1	Group 2	Group 3
Group 1 (n = 27, **6**)	21	3 (**3**)	3 (**3**)
Group 2 (n = 17, **11**)		9 (**3**)	8 (**8**)
Group 3 (n = 15, **15**)			15 (**15**)
Total (n = 59, **32**)	21	12 (**6**)	26 (**26**)

[a]Patients were classified into 3 groups based on electrophysiologic findings: Group 1 had dysfunction confined to the macula; Group 2 had macular and generalized cone system dysfunction; Group 3 had macular and both generalized cone and rod system dysfunction.
[b]Numbers in bold show the numbers of patients who demonstrated electrophysiologic evidence of deterioration. An amplitude reduction of over 50% in any electrophysiologic component and/or a peak time shift of over 3 ms for the light-adapted 30 Hz electroretinogram or dark-adapted 11.0 electroretinogram a-wave were considered evidence of significant electrophysiologic deterioration.

respective electrophysiologic traces appear in Figure 2. Patient 17 showed no ERG group transition (Group 1 at baseline and Group 1 at follow-up). ERG transition from Group 2 to Group 3, with clinically significant ERG deterioration, was demonstrated in Patient 42. Patient 53 was in ERG Group 3 at baseline and had evidence of clinically significant ERG deterioration.

• ELECTROPHYSIOLOGIC FINDINGS: The electrophysiologic findings are summarized in Supplemental Table 4 (available at AJO.com). PERG P50 components were undetectable (93%, 51/55) or moderately reduced (7%, 4/55; Patients 16, 24, 42, and 55) at baseline, in keeping with severe or moderately severe macular dysfunction; and were undetectable in 53 individuals (96%, 53/55) or moderately reduced in 2 patients (4%, 2/55; Patients 16 and 24) at follow-up. There were no available PERG data both at baseline and at follow-up in 2 subjects (Patients 7 and 23), and no available baseline PERGs in 2 further individuals (Patients 45 and 46), who had undetectable PERGs at follow-up.

Complete ERG data sets were available at baseline and follow-up, with few exceptions (Supplemental Table 4). The dark-adapted 0.01 and dark-adapted 11.0 ERGs were abnormal in 11 and 15 patients (20%, 11/54 and 25%, 15/59), respectively, at baseline, and in 22 and 24 subjects (36%, 22/59 and 41%, 24/59), respectively, at follow-up. All those with abnormal dark-adapted 0.01 ERGs had abnormal light-adapted 30 Hz and light-adapted 3.0 ERGs. Three out of 4 patients (Patients 53-56) with undetectable dark-adapted 0.01 responses at follow-up had undetectable light-adapted ERGs at baseline and at follow-up.

Light-adapted 30 Hz and light-adapted 3.0 ERGs were abnormal in 29 and 26 patients (49%, 29/59, and 45%, 26/58), respectively, at baseline; and in 38 and 36 subjects (64%, 38/59 and 61%, 36/59), respectively, at follow-up. An abnormal light-adapted 3.0 ERG was the only baseline ERG abnormality in 2 patients (Patients 29 and 41); isolated light-adapted 30 Hz ERG abnormality occurred in another 4 subjects (Patients 28, 30, 42, and 48). All 6 of these patients showed abnormal responses in both light-adapted tests at follow-up. Isolated light-adapted 30 Hz ERG abnormality occurred in another 2 patients at follow-up.

Four out of 5 sibships were concordant (the same ERG group) both at baseline and at follow-up (Patients 11 and 14; 40 and 42; 45 and 46; 53-55). Two siblings from 1 family had discordant ERG groups, with 1 sibling in Group 3 at baseline and follow-up and the other sibling in Group 2 at baseline and follow-up (Patients 47 and 29) (Supplemental Table 4).

The clinical features of each baseline group are summarized in Table 3 and Figure 3. There was a statistically significant difference between Groups 1 and 3 and between Groups 2 and 3 in terms of onset of disease (Supplemental Table 5, available at AJO.com). There was also

TABLE 3. Clinical Features Associated With Electrophysiologic Group at Baseline, Electrophysiologic Deterioration, and Genotype Group in 59 Patients With Stargardt Disease

		Median Age of Onset (y)	Median Age		Median logMAR Visual Acuity	
			BL	FL	BL	FL
Baseline electrophysiologic group	Group 1 (n = 27)	24.9	34.4	45.0	0.78	1.00
	Group 2 (n = 17)	20.4	29.6	39.4	1.00	1.00
	Group 3 (n = 15)	14.0	29.1	40.3	1.25	1.30
Evidence of clinically significant electrophysiologic deterioration[a]	Stable (n = 27)	23.4	33.5	43.8	0.78	1.00
	Significant deterioration (n = 32)	18.7	30.1	40.8	1.00	1.19
Genotype grouping[b]	Genotype A (n = 19)	17.6	32.6	42.1	1.08	1.39
	Genotype B (n = 10)	22.3	35.7	48.2	0.84	0.94
	Genotype C (n = 18)	20.0	27.8	38.4	0.90	1.20
	Genotype D (n = 12)	26.1	32.7	43.5	0.69	1.19
	Total (n = 59)	20.8	31.7	42.2	0.93	1.22

BL = baseline; FL = follow-up; logMAR = logarithm of minimal angle of resolution.

[a]The subset without evidence of significant deterioration is described as "Stable."

[b]Each patient was classified into 4 mutually exclusive genotype groups on the basis of the molecular analysis: (A) patients with at least 1 null variant, (B) subjects with 2 or more non-null variants, (C) individuals with 1 non-null variant, and (D) patients with no detectable variants.

a statistically significant difference in logMAR VA between Groups 1 and 3 and between Groups 2 and 3. No statistically significant difference was seen between groups with respect to age at baseline, duration of disease, and follow-up interval. Mean yearly electrophysiologic progression within each baseline ERG group with respect to dark-adapted 11.0 a-wave and light-adapted 30 Hz is summarized in Table 4 and Figure 3. Statistical analysis revealed a significant difference between Groups 1 and 3 and between Groups 2 and 3 in terms of yearly amplitude reduction of dark-adapted 11.0 a-wave (Supplemental Table 5). There was also a statistically significant difference in light-adapted 30 Hz yearly peak time shift between Groups 1 and 3. No significant difference was seen between groups with respect to amplitude reduction in light-adapted 30 Hz.

Thirty-two patients showed evidence of clinically significant electrophysiologic deterioration (Table 2 and Supplemental Table 4). Twenty-one subjects showed a greater than 50% amplitude reduction and 26 patients had more than a 3 ms peak time shift (Supplemental Table 4). The clinical findings were compared between the subset of patients with evidence of ERG progression and those without (stable ERG) (Table 3 and Figure 4). There was a statistically significant difference between the 2 subsets in terms of age of onset and logMAR VA at baseline (Supplemental Table 5 and Figure 4). There were no statistically significant differences between the 2 subsets with respect to age at baseline, duration of disease, interval of follow-up, and reduction in logMAR VA (Supplemental Table 5 and Figure 4).

There was clinically significant deterioration of ERG parameters in 22% (6/27) of patients in ERG Group 1, 65% (11/17) in Group 2, and 100% (15/15) in Group 3 (Table 2). Patients with a Group 1 ERG phenotype both at baseline and at follow-up did *not* show significant electrophysiologic deterioration (78%, 21/27), with the Group 1 subjects (22%, 6/27) who did show ERG progression all moving to either Group 2 or Group 3 in equal proportions. Mean yearly electrophysiologic progression was compared between patients with and without clinically significant ERG deterioration (Table 4 and Figure 4). Statistical analysis revealed a significant difference in terms of both amplitude reduction and peak time shift of dark-adapted 11.0 a-wave (Supplemental Table 5 and Figure 4). There was also a statistically significant difference in light-adapted 30 Hz peak time shift. No significant difference was seen with respect to rate of amplitude reduction in light-adapted 30 Hz (Supplemental Table 5).

◦ MOLECULAR GENETICS: Likely disease-causing variants in *ABCA4* were detected in 47 out of 59 patients, with 2 or more variants identified in 22 patients and 1 variant in 25 subjects (Table 1 and Supplemental Table 6, available at AJO.com). Nineteen patients had at least 1 null variant, 10 subjects had 2 or more non-null variants, 18 individuals were identified with 1 non-null variant, and 12 patients had no detectable variants. Detailed results, including *in silico* analysis to assist in the prediction of pathogenicity of the variants, are shown in Supplemental Table 7 (available at AJO.com).

Thirty-eight different variants were found in 47 patients: 11 null mutations with 3 predicted to affect splicing, and 27 non-null variants (Supplemental Tables 6 and 7). Eighteen patients harbored at least 1 null variant, with a single subject having 2 null mutations. Thirty-two of these 38 variants have been previously reported and 6 are putative novel mutations: (1) c.1317G>A, p.Trp439*, (2) c.2103G>A, p.Val675Ile, (3) c.2239delC, p.Leu747Cysfs*787, (4) c.4363C>T,

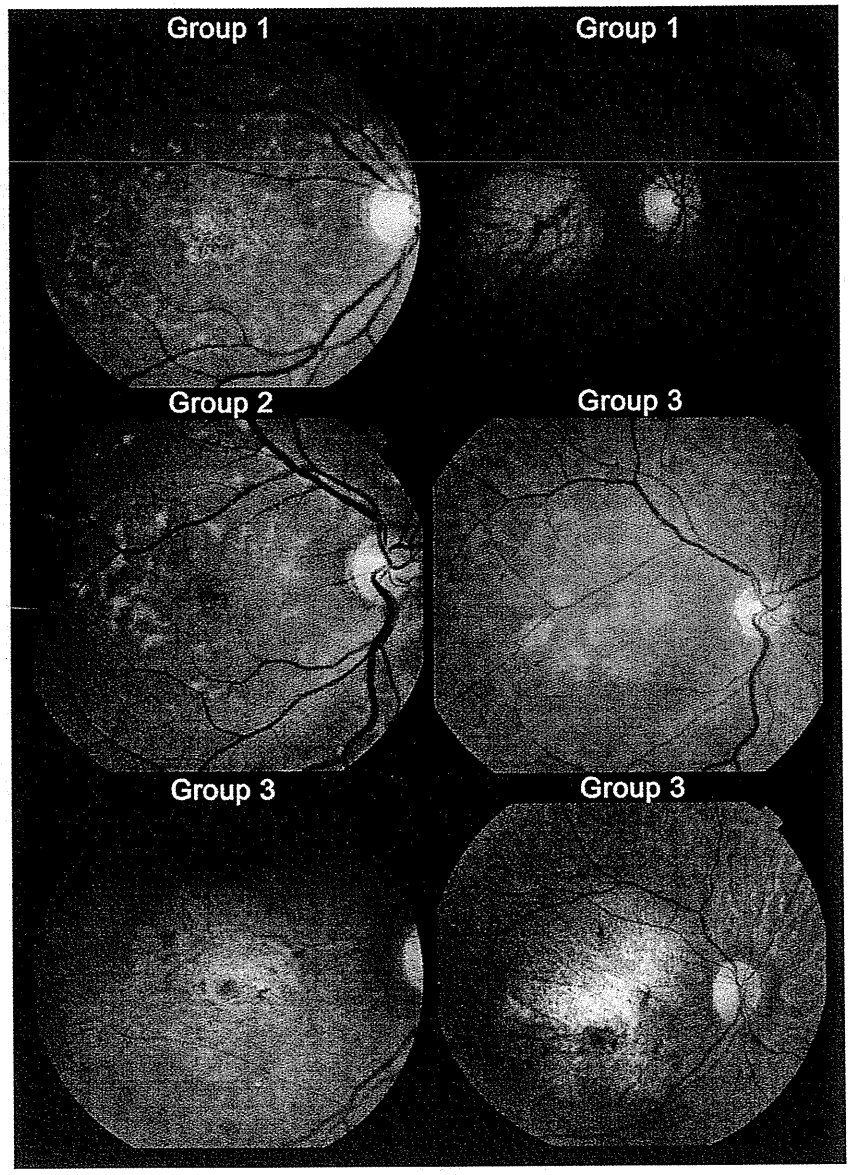

FIGURE 1. Fundus photographs of 3 representative cases of Stargardt disease (Patients 17, 42, and 53) at baseline and at follow-up depicting change over time, with the electrophysiologic group at each time point annotated. (Top) Color fundus photographs of Patient 17 showing macular atrophy surrounded by flecks at baseline (left) and severe well-defined macular atrophy surrounded by atrophic flecks at follow-up (right). Neither electrophysiologic group transition (Group 1 both at baseline and at follow-up) nor clinically significant electrophysiologic deterioration was observed in Patient 17. (Middle) Patient 42 had foveal mottling surrounded by confluent flecks at baseline (left) and multiple areas of macular atrophy at follow-up (right). Electrophysiologic transition from Group 2 to 3, with clinically significant electrophysiologic deterioration, was observed in Patient 42. (Bottom) Patient 53 had multiple areas of macular atrophy with mild pigmentation at baseline (left) and more marked macular atrophy and pigmentation at follow-up (right). Patient 53 was in Group 3 at baseline and experienced clinically significant electrophysiologic deterioration.

p.Cys1455Arg, (5) c.4519G>A, p.Gly1507Arg, and (6) c.5516T>C, p.Phe1839Ser (Supplemental Tables 6 and 7). At least 1 variant was identified in 22 patients (81%, 22/27) in ERG Group 1 at baseline, 12 (71%, 12/17) in Group 2, and 13 (87%, 13/15) in Group 3. At least 1 null variant was found in 8 patients (30%, 8/27) in ERG Group 1 at baseline, 4 (24%, 4/17) in Group 2, and 7 (47%, 7/15) in Group 3 (Supplemental Table 6 and Supplemental Figure 1, available at AJO.com).

• GENOTYPE-PHENOTYPE CORRELATIONS: Clinical features at baseline and electrophysiologic progression in dark-adapted

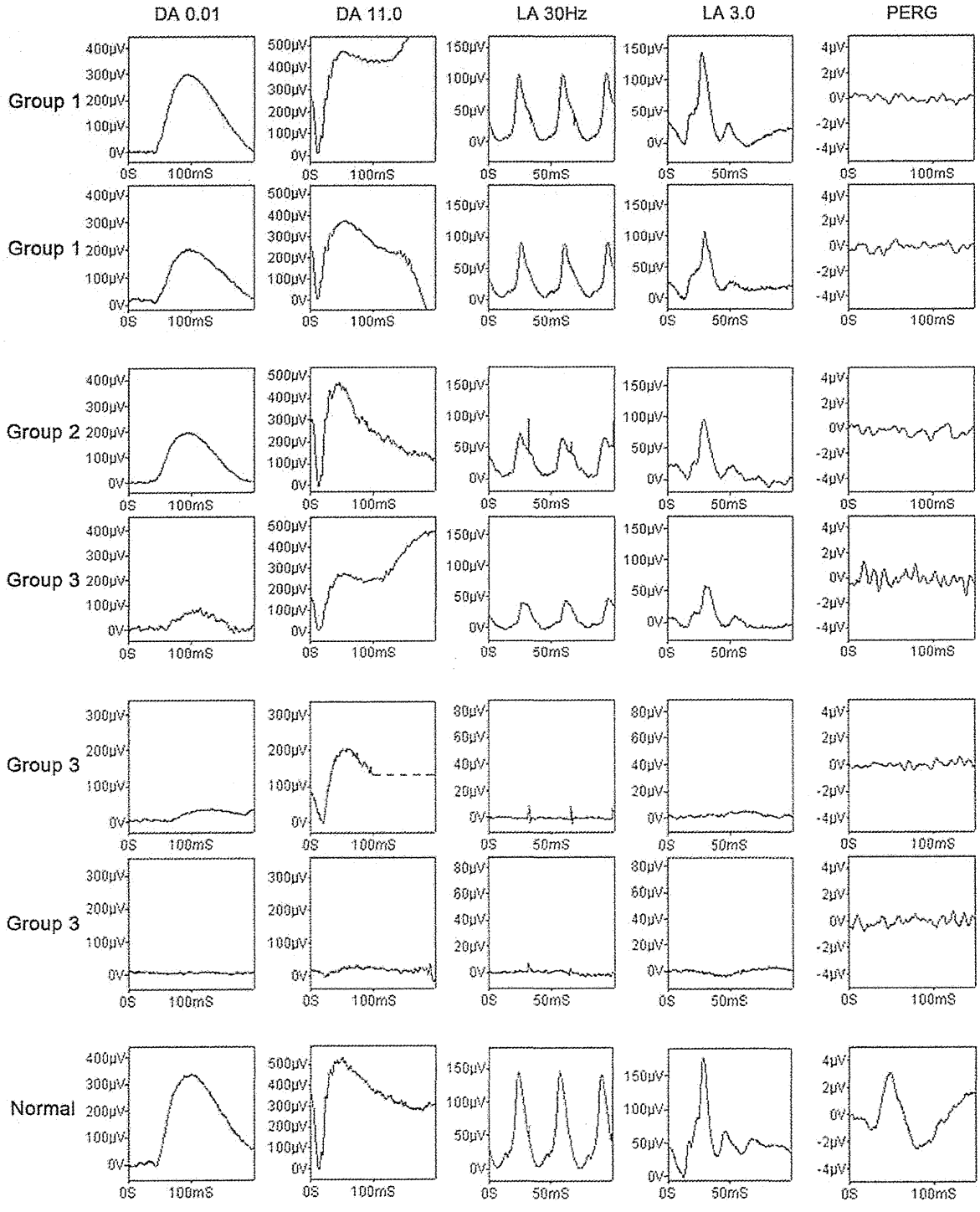

FIGURE 2. Full-field electroretinograms and pattern electroretinograms at baseline and at follow-up from the 3 representative cases of Stargardt disease illustrated in Figure 1 (Patients 17, 42, and 53). Patient 17 demonstrates undetectable pattern electroretinogram (PERG) and normal full-field electroretinograms (ERG) both at baseline (Top row) and at follow-up (Second row), consistent with ERG Group 1 both at baseline and at follow-up. Patient 42 has undetectable PERG and abnormal responses in light-adapted (LA) 3.0, while responses in dark-adapted (DA) 0.01, DA 11.0, and LA 30 Hz are normal at baseline (Third row). At follow-up, all the components of the ERGs are abnormal (Fourth row). Patient 42 demonstrates transition from ERG Group 2 to Group 3, with clinically significant electrophysiologic deterioration observed in rod-derived ERGs. Patient 53 at baseline shows undetectable responses for PERG, LA 30 Hz, and LA 3.0, with abnormal but detectable DA 0.01 and DA 11.0 responses (Fifth row), consistent with ERG Group 3. At follow-up there is only residual ERG activity in the DA 11.0 ERG, representing marked deterioration (Sixth row). (Bottom row) Normal traces are shown for comparison.

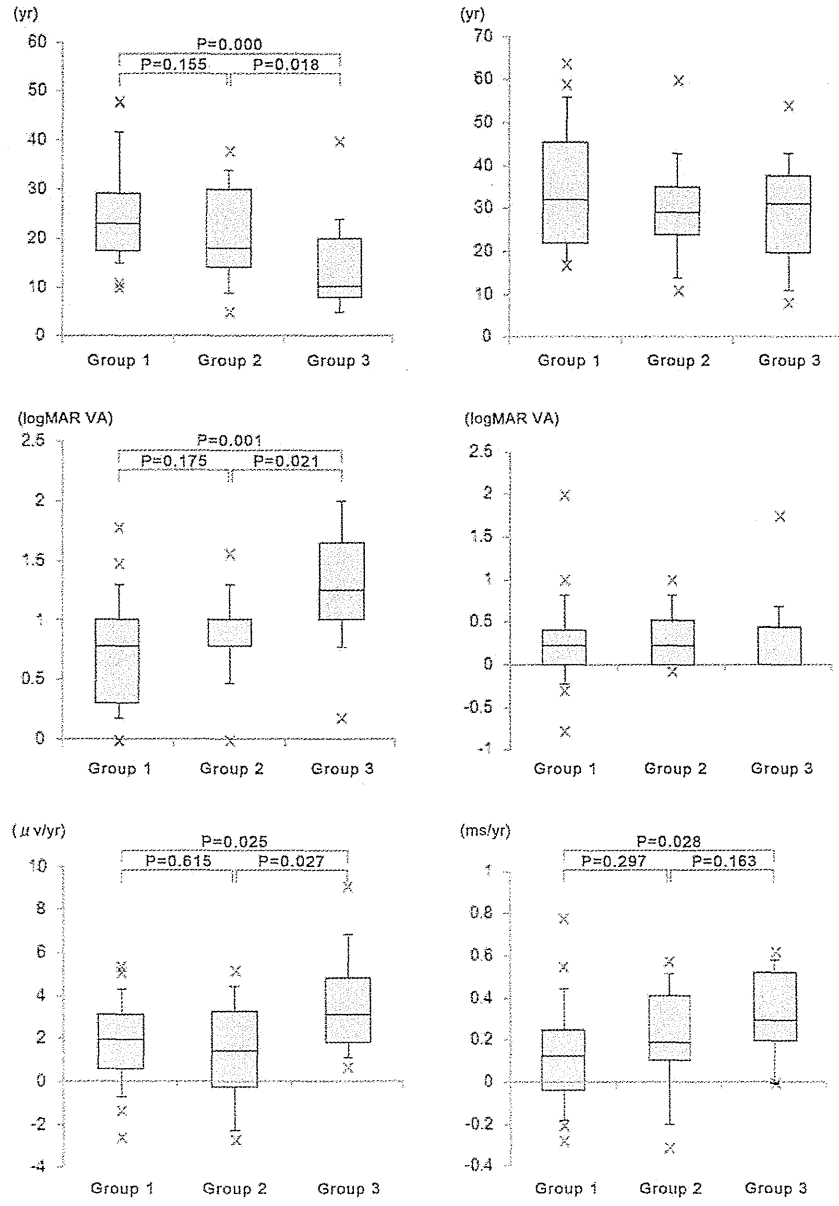

FIGURE 3. A comparison of selected clinical features and electrophysiologic findings associated with each electrophysiologic group at baseline in Stargardt disease, showing significant differences in age of onset, visual acuity at baseline, and electrophysiologic parameters between groups. Age of onset (Top left), age at baseline (Top right), logMAR visual acuity at baseline (Middle left), logMAR visual acuity reduction (Middle right), amplitude reduction per year in the a-wave of the dark-adapted (DA) 11.0 electroretinogram (ERG) (Bottom left), and peak time shift per year in the light-adapted 30 Hz flicker ERG (Bottom right) for the 3 electrophysiologic groups. The boxes show the median and 25% and 75% confidence intervals (lower and upper quartiles). The whiskers extend to what could be considered the 95% confidence interval. Crosses represent values outside the 95% confidence interval. *P* values obtained with the Mann-Whitney *U* test are shown for the parameters in which the Kruskal-Wallis test revealed significant differences. logMAR = logarithm of minimal angle of resolution.

11.0 a-wave and light-adapted 30 Hz of each genotype group are summarized in Tables 3 and 4. There was no statistically significant association identified between the severity of genotype and the extent of electrophysiologic dysfunction on the basis of baseline ERG grouping ($\gamma = -0.126$), although patients with 2 or more non-null variants (genotype B group) less frequently had rod ERG involvement (Table 5 and Supplemental Figure 1).

The distribution of patients with clinically significant electrophysiologic deterioration in each genotype group is

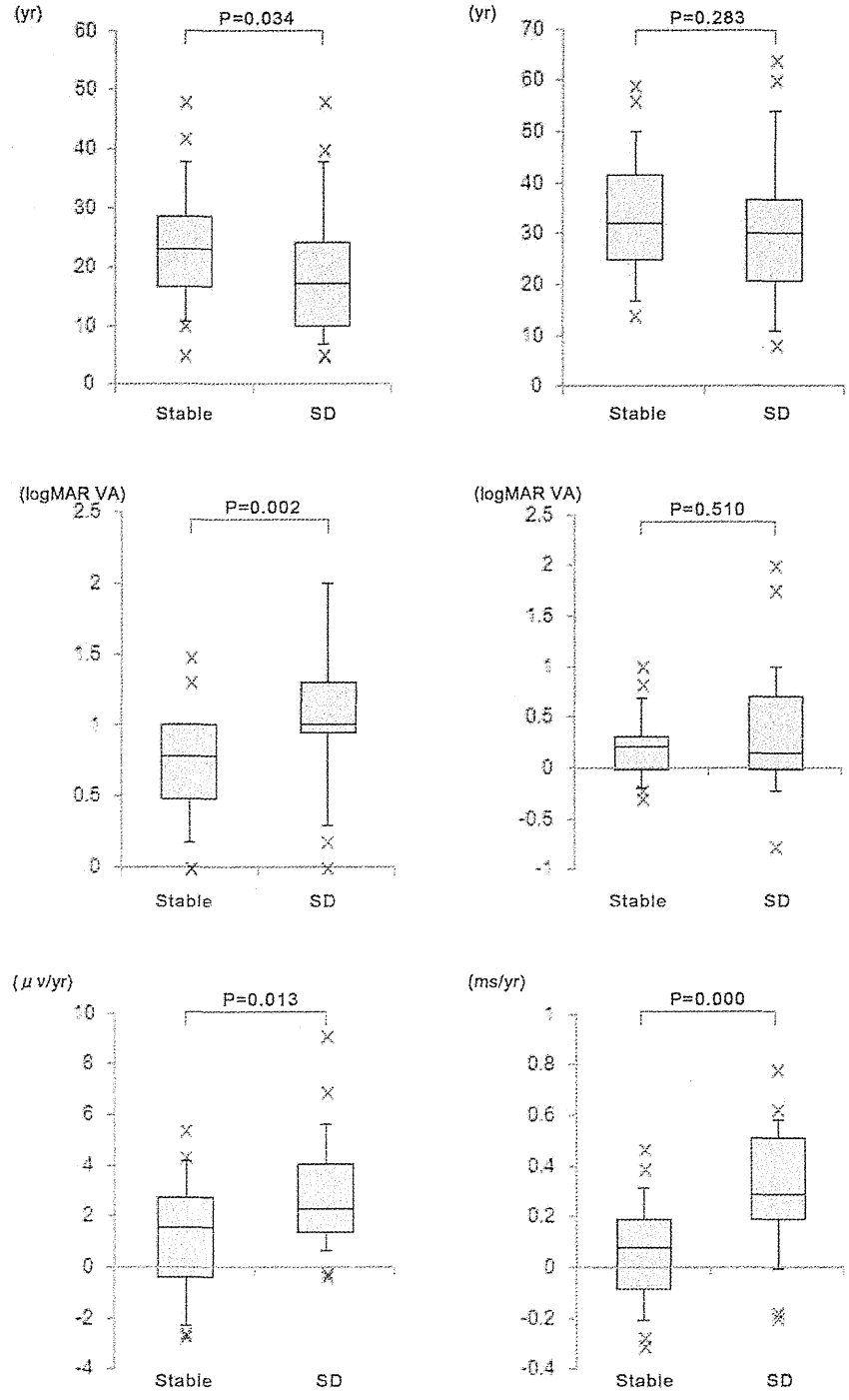

FIGURE 4. A comparison of the clinical findings and electrophysiologic data in Stargardt disease, between the subset of patients with evidence of electroretinogram progression and those without (stable electroretinogram), showing a significant difference in age of onset, visual acuity at baseline, and electrophysiologic parameters between subsets. Age of onset (Top left), age at baseline (Top right), logMAR visual acuity at baseline (Middle left), logMAR visual acuity reduction (Middle right), amplitude reduction per year in the a-wave of the dark-adapted 11.0 electroretinogram (ERG) (Bottom left), and peak time shift per year in light-adapted 30 Hz flicker ERG (Bottom right) for 2 subsets of Stargardt disease (those with and without clinically significant electrophysiologic deterioration). The subset with evidence of clinically significant ERG deterioration is labeled "SD" and the subset without deterioration is labeled "Stable." The boxes show the median and 25% and 75% confidence intervals (lower and upper quartiles). The whiskers extend to what could be considered the 95% confidence interval. Crosses represent values outside the 95% confidence interval. *P* values obtained with the Mann-Whitney *U* test are shown. logMAR = logarithm of minimal angle of resolution.

TABLE 4. Yearly Change[a] in Dark-Adapted Bright Flash Electrophysiologic Responses and Light-Adapted 30 Hz Flicker Responses With Respect to Electrophysiologic Group at Baseline, Electrophysiologic Deterioration, and Genotype Group, in 59 Subjects With Stargardt Disease

	Dark-Adapted 11.0 A-wave			*Light-Adapted 30 Hz*		
	Amplitude Reduction (μV/y)	Percentage Reduction (%/y)	Peak Time Shift (ms/y)	Amplitude Reduction (μV/y)	Percentage Reduction (%/y)	Peak Time Shift (ms/y)
Group 1 (n = 27)	5.5	1.7	0.10	2.7	2.2	0.14
Group 2 (n = 17)	4.5	1.5	0.09	1.1	1.7	0.19
Group 3 (n = 15)	4.9	3.6	0.18	1.5	3.1	0.32
Stable (n = 27)	3.9	1.2	0.04	2.2	1.9	0.07
Electrophysiologic Deterioration (n = 32)	6.0	2.9	0.18	1.7	2.7	0.31
Genotype A (n = 19)	6.5	3.0	0.14	2.3	3.0	0.23
Genotype B (n = 10)	2.3	0.5	-0.01	1.4	0.9	0.12
Genotype C (n = 18)	5.4	2.1	0.16	2.4	3.1	0.33
Genotype D (n = 12)	4.3	2.1	0.09	1.1	0.9	−0.04
Total (n = 59)	5.1	2.1	0.11	1.9	2.3	0.19

Dark-adapted 11.0 = dark-adapted bright flash electroretinogram (flash intensity 11.0 candela seconds (cd·s)/m^2); Light-adapted 30 Hz = light-adapted 30 Hz flicker electroretinogram (flash intensity 3.0 cd·s/m^2).

[a]A yearly amplitude reduction and a yearly percentage reduction were calculated by dividing the amplitude reduction or the percentage reduction by the follow-up time. A yearly peak time shift (difference between peak time at baseline and follow-up) was also calculated by dividing by the follow-up time.

TABLE 5. Distribution of the 4 Genotype Groups With Respect to Electrophysiologic Group at Baseline and Electrophysiologic Deterioration in Stargardt Disease

	Genotype A	Genotype B	Genotype C	Genotype D
Group 1 (n = 27)	8	5	9	5
Group 2 (n = 17)	4	4	4	5
Group 3 (n = 15)	7	1	5	2
Stable (n = 27)	6	9	7	5
Electrophysiologic deterioration (n = 32)[a]	13	1	11	7
Total (n = 59)	19	10	18	12

[a]The subset without evidence of significant deterioration is described as "Stable."

shown in Table 5 and Supplemental Figure 2 (available at AJO.com). Statistical analysis revealed a significant difference between genotype groups A and B and between genotype groups A and C in terms of age of onset. There was also a statistically significant difference between genotype groups A and B with respect to yearly amplitude reduction of dark-adapted 11.0 a-wave and light-adapted 30 Hz yearly peak time shift (Supplemental Table 5). No statistically significant difference was seen between genotype groups and the other ERG parameters (Supplemental Table 5).

Interestingly, 8 of the 9 patients harboring the variant c.5461-10 T>C (Patients 5, 25, 36, 39, 48, 50, 53-55) had clinically significant ERG progression. All 3 unrelated patients (1, 5, and 31) harboring p.Arg943Gln also had p.Gly863Ala, suggesting linkage disequilibrium of these 2 substitutions, with none of these subjects having clinically significant ERG deterioration.

DISCUSSION

THIS REPORT ADDRESSES LONGITUDINAL CHANGES IN CLINical and electrophysiologic features of Stargardt disease in a large, well-characterized cohort of patients, with 1 or both likely disease-causing *ABCA4* alleles identified in 80% of subjects (47/59). The findings confirm the prognostic value of ERG suggested by earlier cross-sectional data and are relevant to the design of future clinical trials.

Approximately one-fifth of Group 1 patients (dysfunction confined to the macula) progressed to either Group 2 or Group 3 (generalized retinal dysfunction) over a mean time period of 10.5 years, whereas 47% of subjects with Group 2 ERG at baseline changed to Group 3 over the same time period. Overall, there was clinically significant electrophysiologic deterioration in 54% of all patients (32/59), with progression in 22% (6/27) of Group 1 subjects, 65% (11/17) of Group 2, and 100% (15/15) of Group 3. These ERG changes far exceed estimates of normal age-related ERG decline.[39] Thus all patients with initial rod involvement (Group 3) demonstrated clinically significant electrophysiologic deterioration, but only 22% of the patients with normal ERGs (Group 1) at baseline showed clinically significant progression.

A transition in ERG group was seen in 14 patients, with all 14 also meeting the criteria for clinically significant

electrophysiologic deterioration. The 3 patients who progressed from Group 1 to Group 2 had abnormal light-adapted 30 Hz ERGs without any abnormalities in light-adapted 3.0 ERGs; the 30 Hz flicker ERG is known to be a more sensitive indicator of altered cone function than the single-flash photopic ERG. In contrast, both cone full-field ERGs were abnormal in the 3 patients who progressed from Group 1 to Group 3. All 6 patients had a >3 ms peak time shift over time; careful observation of the light-adapted 30 Hz ERGs is important in monitoring Stargardt disease patients with normal ERGs. All but 1 patient with abnormalities in dark-adapted 0.01 or dark-adapted 11.0 had abnormal cone responses, suggesting that generalized cone system dysfunction precedes generalized rod system dysfunction, as has previously been demonstrated.[31]

All 5 patients with undetectable cone responses at follow-up had a >50% amplitude reduction in dark-adapted 11.0 during follow-up. Four patients still had residual responses in dark-adapted 11.0 at follow-up and 1 patient had residual responses in dark-adapted 11.0 at baseline, which became undetectable at follow-up. These findings lend further support to the belief that generalized cone system function is abolished before generalized rod system loss, and that the amplitude of dark-adapted 11.0 responses may be helpful in assessing residual retinal function in cases with very severe retinal dysfunction.

The clinical characteristics of each ERG group showed a statistically significant difference between Groups 1 and 3 and Groups 2 and 3 in terms of age of onset, in keeping with the original cross-sectional data, with a younger age of onset associated with more generalized retinal dysfunction.[31] There was also a statistically significant difference in logMAR VA between Groups 1 and 3 and Groups 2 and 3, with worse VA associated with increasingly severe generalized retinal dysfunction, as has been previously proposed.[31] No statistically significant differences were observed between groups with respect to other parameters, including age at baseline, duration of disease, and interval of follow-up. In addition, the age of onset was earlier in subjects who had clinically significant ERG progression compared to those who did not meet criteria for clinically significant deterioration, further supporting the likelihood that age of onset in Stargardt disease is of prognostic value.[7] For ease of comparison between groups, a linear longitudinal relationship has been assumed and the rate of change expressed in terms of yearly amplitude reduction, yearly percentage reduction, and yearly peak time shift. This study has not examined the linearity of change between baseline and follow-up testing; a prospective study with additional, more frequent time point sampling will help address this pertinent question. It is likely that progression will be linear in some individuals and nonlinear in others, in keeping with the commonplace phenotypic heterogeneity of inherited retinal disorders.

ABCA4 mutations were originally reported in patients with autosomal recessive Stargardt disease but shortly thereafter were identified in association with cone dystrophy, cone-rod dystrophy, and "retinitis pigmentosa," with a genotype-phenotype relationship having been proposed.[10,13–15,21,24,40–43] In the present cohort, 82% of patients (22/27) in ERG Group 1 at baseline, 70% (12/17) in Group 2, and 87% (13/15) in Group 3 harbored at least 1 *ABCA4* variant.

A likely disease-causing *ABCA4* variant was identified in 47 out of 59 patients, with 6 putative novel mutations detected. There was no statistically significant association identified between the category of genotype and the extent of electrophysiologic dysfunction on the basis of ERG group, although patients with 2 or more non-null variants (genotype B group) less frequently had rod ERG involvement. A statistically significant greater percentage of patients with null variants (genotype A group) (68%, 13/19) had ERG deterioration, in comparison with patients harboring 2 or more non-null variants (10%, 1/10), with the majority therefore having a stable ERG (90%, 9/10). There was also a statistically significant difference between genotype groups A and B with respect to yearly amplitude reduction of dark-adapted 11.0 a-wave and light-adapted 30 Hz yearly peak time shift. There are several factors that may account for the relative lack of more clearly demonstrable genotype-phenotype correlations, including the relatively small sample size, the fact that only 1 disease-causing allele was identified in most cases, and the vast allelic heterogeneity of *ABCA4*. However, one particular variant (c.5461-10T>C) was found to be associated with electrophysiologic progression. This mutation has been previously reported to be associated with severe disease in both the homozygous and compound heterozygous states,[42,44] suggesting that it may be a marker for more severe disease, which is likely to show clinically significant progression.

Co-inheritance of p.Arg943Gln and p.Gly863Ala has been previously reported,[44,45] with p.Arg943Gln thought to be a benign polymorphism[29,45] and p.Gly863Ala believed to be associated with milder phenotypes,[42,45] although there has been a single report of a severe phenotype associated with p.Gly863Ala in the homozygous configuration.[44] Only 2 out of 8 patients harboring p.Gly863Ala in the present series had evidence of ERG progression, suggesting this variant is indeed likely to be associated with milder disease.

The longitudinal study described herein has identified that a patient's allocation to an individual ERG group, as proposed in the original cross-sectional study, may change over time—a conclusion that could not be made previously because of the inherent limitations of a cross-sectional survey. The rate of progression between groups and within groups has been determined, and age of onset and, to a lesser extent, visual acuity may predict the degree of eventual generalized retinal dysfunction and/or progression. It is important that only 20% of those patients with initially normal full-field ERGs showed evidence of progression

over a 10-year period, compared to 100% of those with an initial rod system ERG abnormality. These data assist the counseling of the patient in relation to visual prognosis and may inform the design, patient selection, and monitoring of current and future clinical trials for *ABCA4*-related retinopathy.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported. Publication of this article was supported by grants from the National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and University College London, Institute of Ophthalmology (UK), Fight For Sight (UK), Moorfields Eye Hospital Special Trustees (UK), Macular Disease Society (UK), the Foundation Fighting Blindness (USA), Suzuken Memorial Foundation (Japan), Mitsukoshi Health and Welfare Foundation (Japan), and Daiwa Anglo-Japanese Foundation (Japan). M.M. is supported by an FFB Career Development Award (USA). Contributions of authors: conception and design (K.F., N.L., A.D., A.W., G.H., M.M.); analysis and interpretation (K.F., N.L., A.D., D.M., C.H., E.S., K. Tsunoda., C.B., A.R., A.M., A.W., G.H., M.M.); writing the article (K.F., A.D., A.R., A.W., K. Tsubota., C.B., G.H., M.M.); critical revision of the article (K.F., N.L., A.D., E.S., K.Tsunoda, K.Tsubota, C.B., A.W., G.H., M.M.); final approval of the article (K.F., K. Tsunoda., C.B., A.T., A.W., G.H., M.M.); data collection (K.F., A.D., D.M., C.H., E.S., A.R., A.M., A.W., G.H., M.M.); provision of materials, patients, or resources (K.F., A.R., A.M., A.W., G.H., M.M.); statistical expertise (K.F., K. Tsubota., C.B., M.M.); obtaining funding (K.F., D.M., K. Tsunoda., A.M., A.W., M.M.); literature search (K.F., A.D., D.M., K. Tsunoda., A.R., M.M.); and administrative, technical, or logistic support (K.F., C.H., A.R., M.M.). The authors are grateful to those who contributed to the assembly of the *ABCA4* panel, particularly Naushin Waseem, Bev Scott, Genevieve Wright, Sophie Devery, and Ravinder Chana (University College London, Institute of Ophthalmology, London, United Kingdom). The authors thank Professor Yozo Miyake (Aichi Medical University, Aichi, Japan), Panagiotis Sergouniotis, Rajarshi Mukhopadhyay, Arundhati Dev Borman, Eva Lenassi (University College London, Institute of Ophthalmology, London, United Kingdom), and Jean Andorf (University of Iowa Institute for Vision Research, Howard Hughes Medical Institute, Iowa City, Iowa, USA) for their insightful comments.

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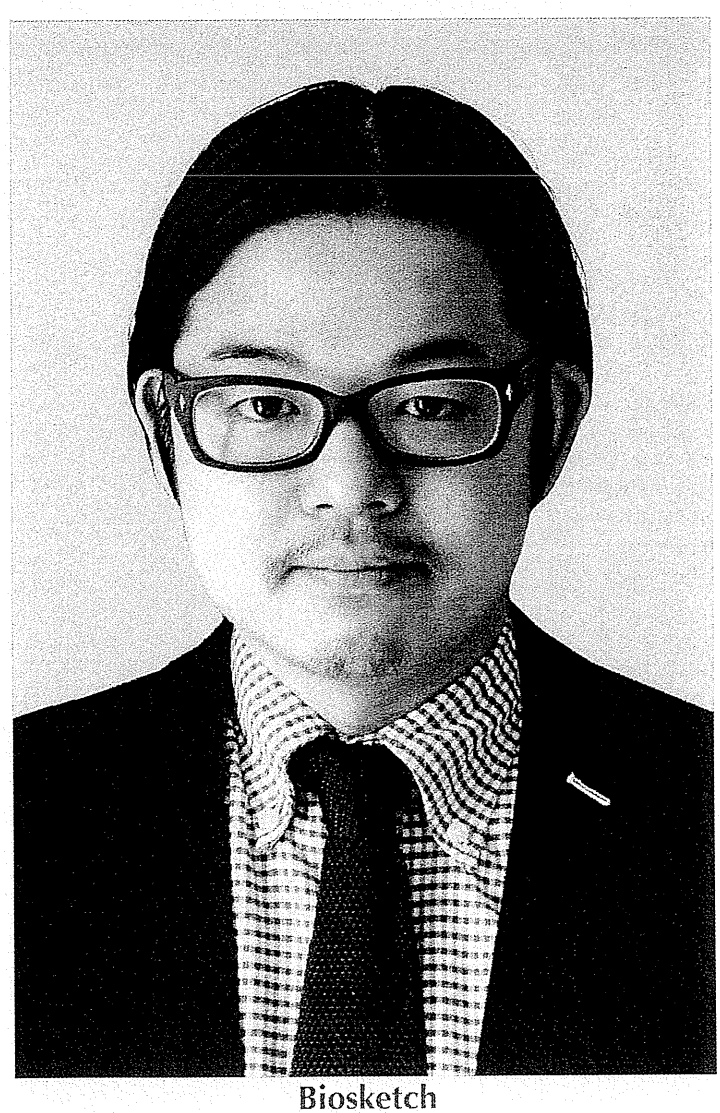

Biosketch

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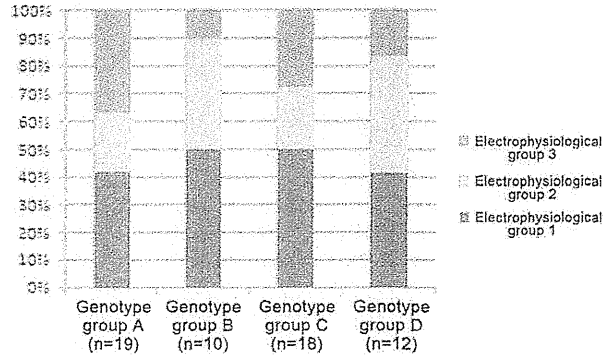
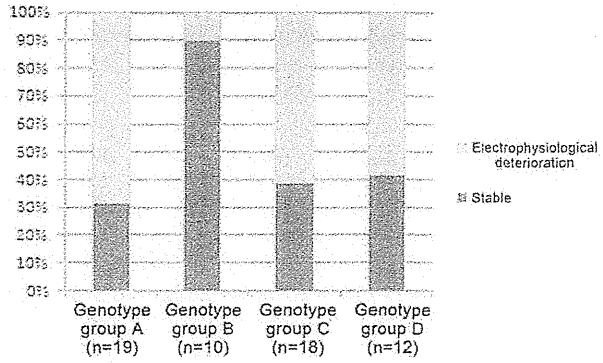


SUPPLEMENTAL FIGURE 1. The association between genotype group and electrophysiologic group at baseline in 59 patients with Stargardt disease, showing that patients with 2 or more null variants (genotype group A) more frequently had generalized rod involvement (electrophysiologic group 3).



SUPPLEMENTAL FIGURE 2. The association between genotype group and presence or absence of clinically significant electrophysiologic deterioration, showing that patients with Stargardt disease harboring 2 or more non-null variants (genotype group B) more frequently have stable electrophysiologic function over time compared with those with more severe mutations (genotype group A).

SUPPLEMENTAL TABLE 1. Normal Ranges for Each Component of International Standard Full-field Electroretinography in Young Adults

	Dark-Adapted 0.01		Dark-Adapted 11.0				Light-Adapted 30 Hz		Light-Adapted 3.0			
			A-wave		B-wave				A-wave		B-wave	
	Amplitude (μV)	Peak Time (ms)	Amplitude (μV)	Peak Time (ms)	Amplitude (μV)	Peak Time (ms)	Amplitude (μV)	Peak Time (ms)	Amplitude (μV)	Peak Time (ms)	Amplitude (μV)	Peak Time (ms)
Age group (<50 years old)	135-455	84-107	250-470	7-14	320-755	39-56	70-200	23-27	30-80	12-15	95-295	27-32

Dark-adapted 0.01 = dark-adapted dim flash electroretinogram with flash intensity 0.01 candela second (cd·s)/m^2; Dark-adapted 11.0 = dark-adapted bright flash electroretinogram with flash intensity 11.0 cd·s/m^2; Light-adapted 30 Hz = light-adapted 30 Hz flicker electroretinogram with flash intensity 3.0 cd·s/m^2; Light-adapted 3.0 = light-adapted 2 Hz electroretinogram with flash intensity 3.0 cd·s/m^2.

SUPPLEMENTAL TABLE 2. Normal Ranges for Full-field Electroretinography in Older Adults

	Dark-Adapted 0.01		Dark-Adapted 11.0				Light-Adapted 30 Hz		Light-Adapted 3.0			
			A-wave		B-wave				A-wave		B-wave	
	Amplitude	Peak Time	Amplitude	Peak Time	Amplitude	Peak Time	Amplitude	Peak Time	Amplitude	Peak Time	Amplitude	Peak Time
Age group (≥50 years old)	30-320	76-117	105-495	10-16	235-665	36-57	50-145	22-29	15-60	12-16	90-220	25-32

Dark-adapted 0.01 = dark-adapted dim flash electroretinogram with flash intensity 0.01 candela second (cd·s)/m^2; Dark-adapted 11.0 = dark-adapted bright flash electroretinogram with flash intensity 11.0 cd·s/m^2; Light-adapted 30 Hz = light-adapted 30 Hz flicker electroretinogram with flash intensity 3.0 cd·s/m^2; Light-adapted 3.0 = light-adapted 2 Hz electroretinogram with flash intensity 3.0 cd·s/m^2.

SUPPLEMENTAL TABLE 3. Primer Sequences and Annealing Temperatures for *ABCA4* Gene Screening

Primer	Sequence (5'–3')	Annealing Temperature (C)
Exon 2 forward	GTGTCTGCTCTGGTTACGTTTTC	61
Exon 2 reverse	CCTTTTGTCTAGAAAGATCTTGGG	
Exon 5 forward	TCCAATCGACTCTGGCTGTT	64
Exon 5 reverse	AGAGATCATGGGGCACAACC	
Exon 9 forward	CCAGCATGGAGTTGAATGAGAC	63
Exon 9 reverse	TAAGTGGACTCTTGCGTTTCCTC	
Exon 10 forward	TTAGATTCTGTCAGCCCAGGAAG	63
Exon 10 reverse	ACCAAGTGGGGTCACTGACTTT	
Exon 15 forward	AGAGAGCCCTTTAGGGCAGAAT	63
Exon 15 reverse	GTTTCCTTGGAAGGGTCCGTAG	
Exon 17 forward	AACTGCGGTAAGGTAGGATAGGG	63
Exon 17 reverse	GACCACCTTTCACAAGTTGCTG	
Exon 30 forward	GCCTAGGGATTTGTCAGCAACT	63
Exon 30 reverse	ACTAAACCAAACTCCCTGCACC	
Exon 38 forward	CCAGTTCACACACATCACCTCAG	63
Exon 38 reverse	ATGAGTGCCACTTTCTTCCTCC	
Exon 39 forward	GTGCTGTCCTGTGAGAGCATCTG	64
Exon 39 reverse	GAGGATTAGGGTGCCTCTGTTTC	
Exon 43 forward	CCCGTGTCAACTGGGACTTAG	63
Exon 43 reverse	ATAGTAGGGTGGCTCTGAGGCC	
Exon 44 forward	GCATTTCTGAAGCCAAATAGGAGA	63
Exon 44 reverse	GTGCATTCTCTTGGAGATGAGAAA	
Exon 46-47 forward	TCTTTACTCTTGGATCCACCTCCT	63
Exon 46-47 reverse	GTGTTCTCCATTGACACTTGGAAG	

SUPPLEMENTAL TABLE 4. Detailed Electrophysiologic Findings of 59 Patients With Stargardt Disease: Electrophysiologic Group, Electrophysiologic Deterioration, and Assessment of Each Component of Full-field Electroretinography

Pt	Selected Eye for Data Analysis	Electrophysiologic Group		Electrophysiologic Deterioration			Dark-Adapted 0.01 (R/L)		Dark-Adapted 11.0 (R/L)		Light-Adapted 30 Hz (R/L)		Light-Adapted 3.0 (R/L)	
		BL	FU	Yes/No	Amplitude Reduction	Peak Time Shift	BL	FU	BL	FU	BL	FU	BL	FU
1	R	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
2	L	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
3	L	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
4	R	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
5	L	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
6	R	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
7	L	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
8	L	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
9	R	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/NA
10	R	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
11	R	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
12	L	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
13	L	1	1	—	—	—	N/N	N/N	N/N	N/N	NA/N	NA/N	N/N	N/N
14	L	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
15	R	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
16	R	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
17	L	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
18	L	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	NA/N	NA/N
19	L	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
20	R	1	1	—	—	—	N/N	N/N	N/N	N/N	N/N	N/N	N/N	N/N
21	L	1	1	—	—	—	NA/NA	N/N	N/N	N/N	N/N	N/N	N/N	N/N
22	R	1	2	✓	—	✓	N/N	N/N	N/N	N/N	N/N	A/A	N/N	A/A
23	L	1	2	✓	—	✓	N/N	N/N	N/N	N/N	N/N	A/A	N/N	N/N
24	R	1	2	✓	—	✓	N/N	N/N	N/N	N/N	N/N	A/A	N/N	N/N
25	R	1	3	✓	✓	✓	N/N	N/A	N/N	N/A	N/N	A/A	N/N	A/A
26	L	1	3	✓	—	✓	N/N	N/N	N/N	A/A	N/N	A/A	N/N	A/A
27	L	1	3	✓	✓	✓	N/N	A/A	N/N	N/N	N/N	A/A	N/N	A/A
28	R	2	2	—	—	—	N/N	N/N	N/N	N/N	A/A	A/A	N/N	A/A
29	R	2	2	✓	✓	✓	N/N	N/N	N/N	N/N	N/N	A/A	A/A	A/A
30	L	2	2	—	—	—	N/N	N/N	N/N	N/N	A/A	A/A	N/N	A/A
31	L	2	2	—	—	—	N/N	N/N	N/N	N/N	A/A	A/A	A/A	A/A
32	R	2	2	—	—	—	NA/NA	N/N	N/N	N/N	A/A	A/A	A/A	A/A
33	L	2	2	✓	—	✓	N/N	N/N	N/N	N/N	A/A	A/A	NA/NA	A/A
34	R	2	2	—	—	—	N/N	N/N	N/N	N/N	A/A	A/A	A/A	A/A
35	R	2	2	—	—	—	N/N	N/N	N/N	N/N	A/A	A/A	A/A	A/A
36	L	2	2	✓	✓	—	N/N	N/N	N/N	N/N	A/A	A/A	A/A	A/A

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SUPPLEMENTAL TABLE 4. Detailed Electrophysiologic Findings of 59 Patients With Stargardt Disease: Electrophysiologic Group, Electrophysiologic Deterioration, and Assessment of Each Component of Full-field Electroretinography (*Continued*)

Pt	Selected Eye for Data Analysis	Electrophysiologic Group		Electrophysiologic Deterioration			Dark-Adapted 0.01 (R/L)		Dark-Adapted 11.0 (R/L)		Light-Adapted 30 Hz (R/L)		Light-Adapted 3.0 (R/L)	
		BL	FU	Yes/No	Amplitude Reduction	Peak Time Shift	BL	FU	BL	FU	BL	FU	BL	FU
37	L	2	3	✓	✓	✓	N/N	N/N	N/N	A/A	A/A	A/A	A/A	A/A
38	L	2	3	✓	✓	✓	N/N	A/A	N/N	A/A	A/A	A/A	A/A	A/A
39	R	2	3	✓	—	✓	N/N	NA/NA	N/N	A/A	A/A	A/A	A/A	A/A
40	L	2	3	✓	✓	✓	N/N	A/A	N/N	A/A	N/N	A/A	A/A	A/A
41	R	2	3	✓	—	✓	N/N	A/A	N/N	A/A	N/N	A/A	N/A	A/A
42	L	2	3	✓	✓	—	N/N	A/A	N/N	A/A	A/A	A/A	N/N	A/A
43	L	2	3	✓	✓	—	N/N	A/A	N/N	A/A	A/A	A/A	A/A	A/A
44	R	2	3	✓	✓	✓	N/N	A/A	N/N	A/A	A/A	A/A	A/A	A/A
45	R	3	3	✓	✓	✓	NA/NA	A/A	A/A	A/A	A/A	A/A	A/A	A/A
46	L	3	3	✓	—	✓	NA/NA	N/N	A/A	A/A	A/A	A/A	A/A	A/A
47	R	3	3	✓	—	✓	NA/NA	A/A	A/A	A/A	A/A	A/A	A/A	A/A
48	R	3	3	✓	✓	—	N/N	A/A	N/A	A/A	A/A	A/A	N/N	A/A
49	L	3	3	✓	✓	✓	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A
50	R	3	3	✓	✓	✓	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A
51	R	3	3	✓	—	✓	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A
52	L	3	3	✓	✓	✓	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/ND
53	L	3	3	✓	✓	✓	A/A	ND/ND	A/A	A/A	ND/ND	ND/ND	ND/ND	ND/ND
54	R	3	3	✓	✓	✓	A/A	ND/ND	A/A	A/A	ND/ND	ND/ND	ND/ND	ND/ND
55	L	3	3	✓	✓	—	A/A	ND/ND	A/A	A/A	A/A	ND/ND	A/A	ND/ND
56	R	3	3	✓	✓	—	A/A	ND/ND	A/A	ND/ND	ND/ND	ND/ND	ND/ND	ND/ND
57	L	3	3	✓	✓	✓	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A
58	L	3	3	✓	—	✓	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A
59	L	3	3	✓	✓	✓	A/A	A/A	N/A	A/A	N/A	A/A	N/A	A/A

✓ = yes; — = no; A = Abnormal; BL = baseline; Dark-adapted 0.01 = dark-adapted dim flash electroretinogram with flash intensity 0.01 candela second (cd·s)/m^2; Dark-adapted 11.0 = dark-adapted bright flash electroretinogram with flash intensity 11.0 cd·s/m^2; FU = follow-up; L = left; Light-adapted 30 Hz = light-adapted 30 Hz flicker electroretinogram with flash intensity 3.0 cd·s/m^2; Light-adapted 3.0 = light-adapted 2 Hz electroretinogram with flash intensity 3.0 cd·s/m^2; N = normal; NA = not available; ND = not-detectable; Pt = patient; R = right; VA = visual acuity.

SUPPLEMENTAL TABLE 6. Electrophysiologic Group Transition and *ABCA4* Variants[a] Identified in 59 Patients With Stargardt Disease

Pt	Electrophysiologic Group (BL / FU)	Genotype Group	Number of Variants	Exon	Nucleotide Substitution	Amino Acid Change	Screening Method (Yes/No) SSCP	APEX	DS
1	I / I	A	3	6	c.768 G>T	p.Val256Val/ Splice site	✓	✓	—
				17	c.2588 G>C	p.Gly863Ala	✓	✓	—
				19	c.2828 G>A	p.Arg943Gln	—	✓	—
2	I / I	C	1	29	c.4328 G>A	p.Arg1443His	—	✓	—
3	I / I	A	3	**10**	**c.1317 G > A**	**p.Trp439***	—	✓	✓
				17	c.2588 G>C	p.Gly863Ala	—	✓	✓
				43	c.5908 C>T	p.Leu1970Phe	—	✓	✓
4	I / I	C	1	44	c.6079 C>T	p.Leu2027Phe	—	✓	—
5	I / I	A	3	17	c.2588 G>C	p.Gly863Ala	—	✓	—
				19	c.2828 G>A	p.Arg943Gln	—	✓	—
				Int. 38	c.5461-10 T>C	Splice site	—	✓	—
6	I / I	C	1	28	c.4139 C>T	p.Pro1380Leu	—	✓	—
7	I / I	D	0				✓	—	—
8	I / I	B	2	10	c.1253 T>C	p.Phe418Ser	✓	—	✓
				44	c.6079 C>T	p.Leu2027Phe	✓	—	✓
9	I / I	A	2	Int. 28	c.4253+5 G>T	Splice site	✓	✓	—
				30	**c.4519 G > A**	**p.Gly1507Arg**	✓	—	✓
10	I / I	B	2	30	c.4469 G>A	p.Cys1490Tyr	—	✓	✓
				44	c.6089 G>A	p.Arg2030Gln	—	✓	✓
11	I / I	D	0				—	✓	—
12	I / I	C	1	3	c.286 A>C	p.Asn96His	✓	—	—
13	I / I	A	1	30	c.4537_4538insC	p.Gly1513Profs*1554	—	✓	—
14	I / I	D	0				✓	—	—
15	I / I	C	1	46	c.6320 G>A	p.Arg2107His	✓	—	—
16	I / I	D	0				—	✓	—
17	I / I	C	1	3	c.161 G>A	p.Cys54Tyr	✓	—	—
18	I / I	B	2	28	c.4139 C>T	p.Pro1380Leu	—	✓	—
				42	c.5882 G>A	p.Gly1961Glu	—	✓	—
19	I / I	C	1	22	c.3322 C>T	p.Arg1108Cys	✓	—	—
20	I / I	A	2	**10**	**c.1317 G > A**	**p.Trp439***	—	✓	✓
				17	c.2588 G>C	p.Gly863Ala	—	✓	✓
21	I / I	B	3	5	c. 466 A>G	p. Ile156 Val	✓	—	✓
				30	**c. 4363 C > T**	**p. Cys1455Arg**	✓	—	✓
				39	**c. 5516 T > C**	**p. Phe1839Ser**	✓	—	✓
22	I / II	C	1	46	c.6320 G>A	p.Arg2107His	—	✓	—
23	I / II	C	1	17	c.2588 G>C	p.Gly863Ala	—	✓	—
24	I / II	A	1	35	c.4956 T>G	p.Tyr1652*	—	✓	—
25	I / III	A	1	Int. 38	c.5461-10 T>C	Splice site	—	✓	—
26	I / III	D	0				✓	—	—
27	I / III	A	1	22	c.3211_3212insGT	p.Ser1071Cysfs*1084	—	✓	—
28	II / II	A	2	9	c.1222 C>T	p.Arg408*	✓	—	✓
				14	**c.2023 G > A**	**p.Val675Ile**	✓	—	✓
29	II / II	C	1	47	c.6449 G>A	p.Cys2150Tyr	—	—	✓
30	II / II	D	0				—	✓	—
31	II / II	B	3	17	c.2588G>C	p.Gly863Ala	✓	—	—
				22	c.3322 C>T	p.Arg1108Cys	✓	—	—
				19	c.2828 G>A	p.Arg943Gln	✓	—	—
32	II / II	B	2	14	c.1957 C>T	p.Arg653Cys	—	✓	—
				44	c.6089 G>A	p.Arg2030Gln	—	✓	—
33	II / II	D	0				✓	—	—
34	II / II	B	2	17	c.2588 G>C	p.Gly863Ala	✓	—	—
				22	c.3259 G>A	p.Glu1087Lys	✓	—	—

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