

Differential Disease Progression in Atrophic Age-Related Macular Degeneration and Late-Onset Stargardt Disease

Moritz Lindner,¹ Stanley Lambertus,² Matthias M. Mauschitz,¹ Nathalie M. Bax,² Eveline Kersten,² Anna Lüning,¹ Jennifer Nadal,³ Steffen Schmitz-Valckenberg,¹ Matthias Schmid,³ Frank G. Holz,¹ Carel B. Hoyng,² and Monika Fleckenstein¹; for the Foveal sparing Atrophy Study Team (FAST)

¹Department of Ophthalmology, University of Bonn, Bonn, Germany

²Department of Ophthalmology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

³Institute for Medical Biometry, Informatics and Epidemiology, University of Bonn, Bonn, Germany

Correspondence: Monika Fleckenstein, Department of Ophthalmology, University of Bonn, Ernst-Abbe-Str. 2, D-53127 Bonn, Germany; Monika.Fleckenstein@ukb.uni-bonn.de.

ML and SL are joint first authors.

See the appendix for the members of the Foveal sparing Atrophy Study Team (FAST).

Submitted: October 24, 2016

Accepted: January 11, 2017

Citation: Lindner M, Lambertus S, Mauschitz MM, et al. Differential disease progression in atrophic age-related macular degeneration and late-onset Stargardt disease. *Invest Ophthalmol Vis Sci.* 2017;58:1001-1007. DOI:10.1167/iovs.16-20980

PURPOSE. To compare the disease course of retinal pigment epithelium (RPE) atrophy secondary to age-related macula degeneratio (AMD) and late-onset Stargardt disease (STGD1).

METHODS. Patients were examined longitudinally by fundus autofluorescence, near-infrared reflectance imaging, and best-corrected visual acuity (BCVA). Areas of RPE atrophy were quantified using semi-automated software, and the status of the fovea was evaluated based on autofluorescence and near-infrared reflectance images. Mixed-effects models were used to compare atrophy progression rates. BCVA loss and loss of foveal integrity were analyzed using Turnbull's estimator.

RESULTS. A total of 151 patients (226 eyes) with RPE atrophy secondary to AMD and 38 patients (66 eyes) with RPE atrophy secondary to late-onset STGD1 were examined for a median time of 2.3 years (interquartile range, 2.7). Mean baseline age was 74.2 years (SD, 7.6) in AMD and 63.4 (SD, 9.9) in late-onset STGD1 ($P = 1.1 \times 10^{-7}$). Square root atrophy progression was significantly faster in AMD when compared with late-onset STGD1 (0.28 mm/year [SE, 0.01] vs. 0.23 [SE, 0.03]; $P = 0.030$). In late-onset STGD1, the median survival of the fovea was significantly longer when compared with eyes with AMD (8.60 vs. 3.35 years; $P = 0.005$) with a trend to a later BCVA loss of ≥ 3 lines (5.97 vs. 4.37 years; $P = 0.382$).

CONCLUSIONS. These natural history data indicate differential disease progression in AMD versus late-onset STGD1. The results underline the relevance of refined phenotyping in elderly patients presenting with RPE atrophy in regard to prognosis and design of interventional trials.

Keywords: Stargardt disease, age-related macular degeneration, fundus autofluorescence, retinal pigment epithelium, geographic atrophy

Atrophy of the RPE represents a common late-stage manifestation of various retinal diseases, including late-stage dry age-related macula degeneration (AMD) and Stargardt disease (STGD1).¹ In industrialized countries, late-stage neovascular or advanced dry AMD is the leading cause of legal blindness in the elderly.² Although the exact pathogenetic mechanisms leading to geographic atrophy³ are still poorly understood, chronic inflammatory processes, excessive lipofuscin accumulation in the RPE lysosomal compartment, complement system dysregulation, and vascular factors have been implicated in the development of AMD.⁴

In contrast to the multifactorial etiology of AMD, STGD1 is an autosomal recessive retinal dystrophy caused by pathogenic sequence variants in the adenosine triphosphate-binding cassette, subfamily A, member 4 (*ABCA4*, MIM 601691) gene. *ABCA4* encodes an integral transmembrane protein, expressed in retinal photoreceptors. It is involved in the clearance of all-*trans*-retinal aldehyde, a byproduct of the retinoid cycle of vision.⁵ *ABCA4* dysfunction leads to the accumulation of lipofuscin and its constituent, di-retinoid-pyridinium-ethanolamine, finally resulting in RPE atrophy development.^{6,7}

Comparable ages of onset as well as fundoscopic parallels result in a certain risk in confounding AMD and late-onset STGD1.⁸ It is well understood that distinction between both conditions is of practical relevance to an individual patient with regard to genetic counseling. Yet to what extent differentiation between both conditions also influences individual prognosis in terms of visual acuity loss and RPE atrophy progression has not been assessed. Extending our analysis on two recently described cohorts,^{9,10} in the present work we identify significant differences in the course of AMD and late-onset STGD1. These results underline the relevance of refined phenotyping in patients presenting with RPE atrophy. Furthermore, the improved understanding of the distinct kinetic of disease progression will be relevant for emerging therapeutic approaches.

METHODS

Patient Identification

The present study consists of the following two distinct cohorts: patients with RPE atrophy secondary to AMD and



patients with RPE atrophy associated with late-onset STGD1. Inclusion criteria for the current analysis for both cohorts were the following: (1) at least one well-defined contiguous area of RPE atrophy corresponding to areas of reduced fundus autofluorescence (FAF) to an extent of $\geq 0.05 \text{ mm}^2$ (the size of the smallest atrophic area in cases of multifocality) in one or both eyes and (2) clear ocular media allowing for acquisition of high-quality FAF images. For inclusion into the AMD cohort, soft drusen and/or retinal pigment abnormalities consistent with the diagnosis of AMD had to be present. For inclusion into the late-onset STGD1 cohort, patients had to exhibit typical yellow-white flecks or dots correlating with hyperautofluorescent flecks on 488-nm FAF imaging. This FAF pattern had previously been termed “fine granular pattern with peripheral punctate spots (GPS[+]).”^{11,12} The clinical phenotype of late-onset STGD1 was supported by at least one (likely) pathogenic variant in the *ABCA4* (NM_000350.2) gene. The peripherin-2 gene (*PRPH2*; NM_000322.4) was additionally sequenced in patients with fewer than two *ABCA4* (likely) pathogenic variants to exclude autosomal-dominant multifocal pattern dystrophy or central areolar choroidal dystrophy.^{13,14} Patients had to be at least 45 years of age at self-reported symptom onset. Both eyes of a patient were included in the analysis if the inclusion criteria were met. General exclusion criteria for both cohorts were the presence of retinal disease that could possibly confound observations (e.g., diabetic retinopathy, present or past exudative events, idiopathic serous chorioretinopathy).

All of the patients were recruited in the context of the Fundus Autofluorescence in Age-Related Macular Degeneration (FAM) Study or at the outpatient department of Radboud University Medical Center. The study followed the tenets of the Declaration of Helsinki. Approval by the institutional review boards was obtained by each of the participating centers. Informed consent was obtained from each participant after an explanation of the study's nature and possible consequences of participation. Both cohorts have previously been reported elsewhere.^{8–10,12,15}

Assessment of Visual Acuity

At each visit, best-corrected visual acuity (BCVA) was determined using a Snellen or Early Treatment Diabetic Retinopathy Study chart. Visual acuity is reported in logarithm of the minimum angle of resolution (logMAR) notation. Visual acuity of counting fingers was set to 1.8 logMAR and hand motions to 2.2 logMAR.¹⁶

Image Acquisition and Grading

FAF images were acquired using HRA2 or Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany) with an excitation wavelength of 488 nm and an emission spectrum of 500 to 700 nm using the high-speed mode. Near-infrared (NIR) reflectance images were obtained with an excitation wavelength of 820 nm. The field of view was centered on the fovea and set to $30^\circ \times 30^\circ$ or $55^\circ \times 55^\circ$ to fit the entire area of atrophy. Images were acquired with a minimum resolution of 512×512 pixels and single FAF images were automatically aligned and averaged to maximize the signal-to-noise ratio using the manufacturer's software.

Areas of RPE atrophy were measured on FAF images applying image processing software based on gray value detection for semi-automated identification of atrophic RPE areas. Only areas of decreased autofluorescence $> 0.05 \text{ mm}^2$ were considered to represent RPE atrophy.^{17–20} The involvement of the fovea by the atrophic process was determined based on FAF and NIR reflectance images and was graded as

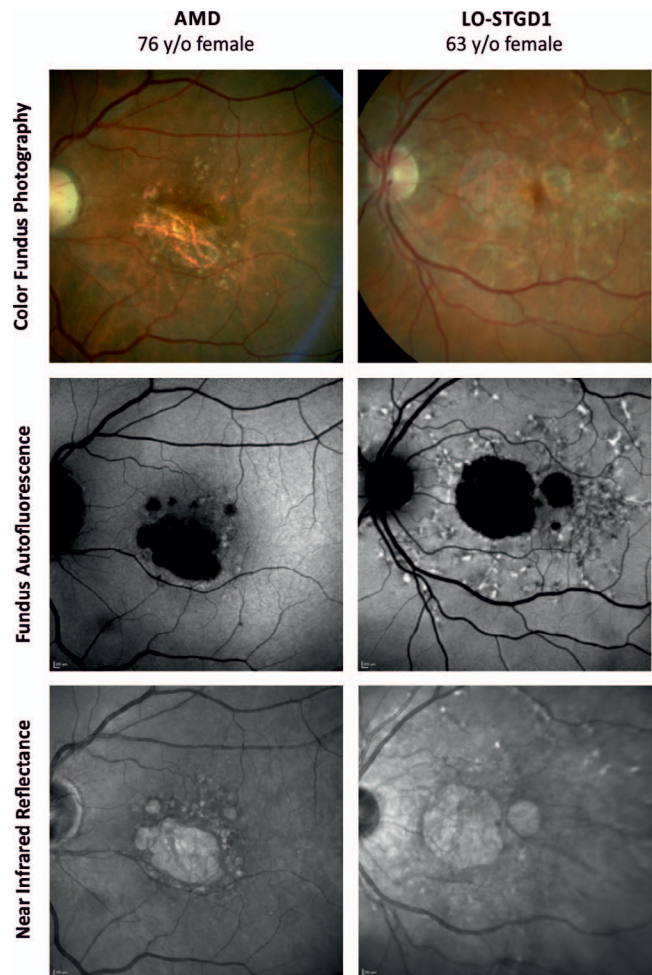


FIGURE 1. Multimodal imaging as performed in this study of representative left eyes of a patient with retinal pigment epithelium atrophy secondary to AMD and a patient with retinal pigment epithelium atrophy secondary to late-onset STGD1.

follows: definitely involved, probably involved, probably not involved, and definitely not involved. For further analysis, these gradings were summarized to “involved” and “not involved.” A representative example of an eye with RPE atrophy secondary to AMD and RPE atrophy secondary to late-onset STGD1 is provided in Figure 1.

Statistical Analysis

The total atrophy size measured for each visit was square-root transformed to reduce the dependency of enlargement rates on baseline lesion size ($\sqrt{\text{area [mm]}}$) as previously suggested.²¹ To quantify atrophy progression rates within the patient collective, a linear mixed-effects model was used as described earlier.^{22,23} The two-level, random-effects model used here separates eye-specific and patient-specific effects and accounts for dependencies between measurements that were obtained from the same patient and/or eye.

The factor “AMD” versus “LO-STGD1” was included as a fixed effect in the model. Backward selection of the other covariates, including higher order interactions, was used to build the final linear mixed-effects model.

Turnbull's estimator²⁴ was used to estimate the percentages of eyes with BCVA loss $\geq 0.3 \text{ logMAR}$ (≥ 3 Early Treatment Diabetic Retinopathy Study chart lines) and $\geq 0.6 \text{ logMAR}$ (≥ 6

TABLE 1. Baseline Characteristics of Patients With AMD and Late-Onset STGD1

Characteristic	AMD		Late-Onset STGD1		P Value
	Patients, <i>n</i>	Mean ± SD, %	Patients, <i>n</i>	Mean ± SD, %	
Gender					
Male	55	36.4	17	44.7	0.449*
Female	96	63.6	21	55.3	
Disease status					
Bilateral RPE atrophy	86	61.4	27	71.1	0.006*
RPE atrophy + NV in fellow eye	39	27.9	2	5.2	
RPE atrophy + “early” changes in fellow eye	15	10.7	9	23.7	
Follow-up time, y	151	2.2† (IQR: 2.6)	38	2.5† (IQR: 3.6)	0.774‡
Age, y	151	74.2 ± 7.6	38	63.4 ± 9.9	<0.001§
	Eyes, <i>n</i>	Mean ± SD, %	Eyes, <i>n</i>	Mean ± SD, %	P Value
Atrophy size, mm ²	226	6.3 ± 5.0	66	6.2 ± 7.3	0.914§
Status of the fovea at baseline					
Not involved	122	54.0	57	86.4	<0.001*
Involved	104	46.0	9	13.6	
Visual acuity, logMAR	226	0.6 ± 0.4	66	0.4 ± 0.4	0.001§

SD, standard deviation; IQR, interquartile range.

* χ^2 test.

† Median.

‡ Mann-Whitney.

§ *t*-test.

Early Treatment Diabetic Retinopathy Study chart lines) from baseline, as previously reported.⁹ A similar approach was used to estimate the percentage of eyes with loss of foveal integrity over time (status transition of the fovea from “not involved” to “involved”). A comparison of the course of BCVA and of the foveal status between AMD versus late-onset STGD1 was performed using the log-rank test.

RESULTS

Patients

A total of 226 eyes (151 patients; 55 males, 96 females) with RPE atrophy secondary to AMD and 66 eyes (38 patients; 17 males, 21 females) with RPE atrophy secondary to late-onset STGD1 were examined over time. At baseline, 113 patients exhibited bilateral RPE atrophy (86 patients with AMD and 27 patients with late-onset STGD1). In 24 patients, the fellow eye had early changes, that is, disease-related alterations without atrophy or neovascularization (15 patients with AMD and nine patients with late-onset STGD1; $P = 0.117$), and 41 patients exhibited neovascularization in the fellow eye (39 patients with AMD and two patients with late-onset STGD1; $P = 0.006$). In 11 patients, only one eye was included because the fellow eyes fulfilled any of the exclusion criteria (e.g., insufficient imaging quality). One eye did not contribute to the analysis because neovascularization developed right after the first visit.

Baseline Characteristics

Mean age at baseline was 74.2 years (SD, 7.6) in the AMD and 63.4 years (SD, 9.9) in the late-onset STGD1 patient cohort. At first presentation, RPE atrophy size in AMD patients was 6.3 mm² (SD, 5.0) and 6.2 mm² (SD, 7.3) in late-onset STGD1 ($P = 0.914$). At baseline, the fovea was graded as “not involved” in 54.0% of eyes (122 of 226 eyes) with AMD and in 86.4% of eyes (57 of 66 eyes) with late-onset STGD1 ($P = 4.1 \times 10^{-6}$). BCVA at baseline was significantly different between both cohorts with

0.6 logMAR (SD, 0.4) in AMD and 0.4 logMAR (SD, 0.5) in late-onset STGD1 ($P = 1.3 \times 10^{-3}$). An overview on baseline characteristics is given in Table 1.

Disease Progression

Data of a total of 897 eye visits were included in the analysis. The median follow-up time was 2.2 years (interquartile range [IQR], 2.6) in AMD and 2.5 years (IQR, 3.6) in late-onset STGD1 ($P = 0.774$). To compare atrophy progression kinetics between AMD and late-onset STGD1, a linear mixed-effects model was used. Average square-root transformed atrophy progression was 0.28 mm/year (SE, 0.01) in AMD, and 0.23 mm/year (SE, 0.03) in late-onset STGD1 ($P = 0.030$). Model results were corrected for distinct age structures between the cohorts by including age as a fixed effect (coefficient estimate: 0.02 ± 0.00 ; $P = 0.011$).

Transition of the status of the fovea from “not involved” to “involved” during the observational period was observed in 48 eyes with AMD (39.3% of eyes with “not involved” fovea at baseline) and in only 5 eyes with late-onset STGD1 (8.8% of eyes with “not involved” fovea at baseline). Notably, the follow-up period in late-onset STGD1 patients was longer than in AMD patients (see earlier). Time-to-event analyses revealed a median time from noninvolvement of the fovea at baseline to foveal involvement of 3.35 years (95% confidence interval [CI], 2.50–4.15) in AMD and 8.60 years (CI, not available) in late-onset STGD1 (Table 2). In parallel, a visual acuity loss of ≥ 3 and ≥ 6 lines, respectively, occurred consistently, although not significantly, later in late-onset STGD1 when compared with AMD (Table 2). Figure 2 shows two representative disease courses in an eye with late-onset STGD1 and an eye with AMD.

DISCUSSION

This study reveals differences between AMD and late-onset STGD1 with respect to both atrophy progression and changes in visual acuity. We found a significantly faster atrophy

TABLE 2. Median Times to Event for Foveal Involvement and Vision Loss in AMD and Late-Onset STGD1

Event	AMD		Late-Onset STGD1		P Value, Log-Rank
	Median, y	CI	Median, y	CI	
Fovea becomes involved	3.35	2.50-4.15	8.60	n.a.	0.005
Visual acuity loss ≥ 3 lines	4.37	2.96-4.37	5.97	4.01-5.97	0.382
Visual acuity loss ≥ 6 lines	7.52	7.52- ∞	33.2% had event after 7.50 years		0.320

CI, confidence interval; n.a., not available.

progression in eyes with AMD along with significantly lower BCVA scores at baseline and faster, albeit not significant, loss of BCVA.

Atrophy progression and visual acuity courses have been previously assessed independently in both AMD and STGD1. Although distinct analytic strategies preclude direct comparisons, our data are overall compatible with previously published values.^{10,25-28} Despite similar lesion size at baseline, patients with late-onset STGD1 had a better BCVA, presumably because their fovea was more frequently intact (86.4% vs. 54% of eyes with AMD). Moreover, they had both atrophy progression kinetics and survival times of the fovea in favor, but the difference in decline in BCVA when compared with AMD was less pronounced. We have recently reported that the parameters “status of the fovea,” “total lesion size,” and the “age at baseline” in eyes with atrophy as a result of AMD have a significant impact on BCVA and that these factors together explain 65% of BCVA variability.⁹ The remaining 35% of BCVA variability may be explained by other factors, such as media opacities and the general mental status. In addition, it may be explained by BCVA test variability itself.⁹

Foveal sparing is observed in several retinal diseases,^{8,10,15,20,29-33} exhibiting a specific pattern of RPE atrophy surrounding an intact foveal island. Although the present study did not differentiate between this typical pattern of foveal sparing and general foveal noninvolvement, patients with a long-term preservation of foveal integrity may develop eventual foveal sparing. Interestingly, eyes with an uninvolved fovea at baseline progressed to foveal atrophy during the review period in almost 40% of eyes with AMD, but only 8.8% of eyes with late-onset STGD1, despite their slightly longer follow-up. Atrophy being more closely to the fovea at first presentation

may be a reason for requiring less time to involve the fovea into the atrophic process in AMD. Another explanation may be a longer foveal survival because of the protecting mechanisms in late-onset STGD1. Yet foveal sparing can be present in phenotypes that are independent of *ABCA4* sequence variants, including AMD,^{8,15,20,29-33} and is infrequent in a general STGD1 population.¹⁵ Therefore, other genetic factors and distinct anatomical, metabolic, and/or biochemical aspects are likely involved.

A further hallmark contrast between both cohorts was the frequency of neovascularization observed in fellow eyes, which was less frequent in late-onset STGD1. For AMD, it has been described that atrophy progression is slower in eyes with a fellow eye exhibiting neovascularization.³⁴ We did not correct for this factor in the linear mixed-effects model. Yet from the available data on AMD,³⁴ we would expect the difference between AMD and late-onset STGD1 to become even larger when correcting for this factor.

Our patients with biallelic—but also with mono-allelic—*ABCA4* variants share an identical phenotype that exhibits typical flecks of increased FAF surrounding the atrophic lesion; it resembles the FAF pattern in patients with typical STGD1. Given the high carrier frequency up to 1:25,³⁵ it is highly unlikely that a single pathogenic *ABCA4* variant can cause this phenotype on its own. In analog, several cases with typical STGD1 are to date also genetically still unsolved by failing to detect a second pathogenic *ABCA4* variant. However, these second “missing” pathogenic variants are now increasingly being found with recent genetic techniques.³⁶ We postulate that either a second sequence variant affecting *ABCA4* function or other genetic factors that lower the total *ABCA4* function are still to be found in our patients with mono-allelic

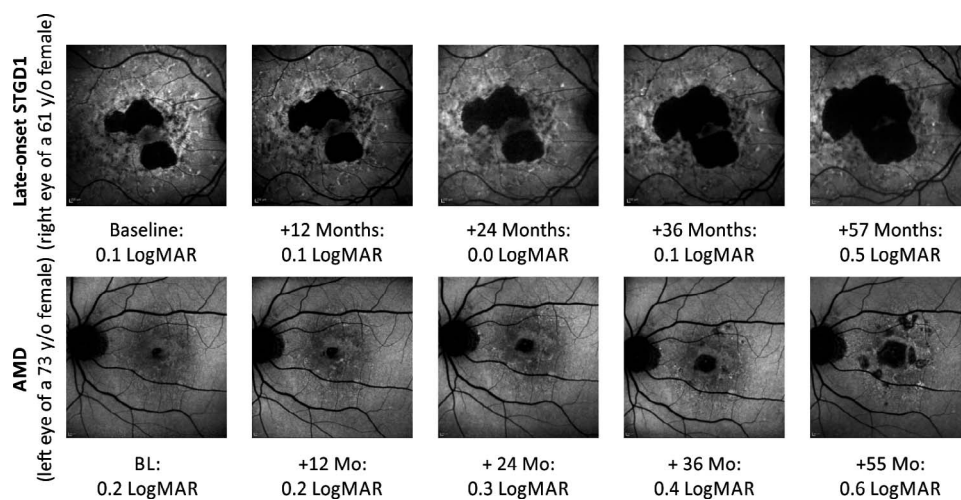


FIGURE 2. Fundus autofluorescence and corresponding visual acuity values of an exemplary course of late-onset STGD1 (upper row) and AMD (lower row). Square root atrophy progression rate in the late-onset STGD1 eye shown is 0.25 mm/year, whereas it is 0.58 mm/year in the AMD eye. Note that the eye with late-onset STGD1 shown has a larger non-square root transformed progression as a result of the larger baseline atrophy size. logMAR, logarithm of the minimum angle of resolution.

ABCA4 variants. They may be sufficient to cause this distinct phenotype at the mild end of STGD1 and in the disease spectrum of AMD. With regard to these hypotheses, recent studies are of particular interest quantifying normal levels of lipofuscin in parents of patients with STGD1.^{37,38} Furthermore, it has also been reported that *abca4*^{-/-} mice show increased levels of some bis-retinoids.³⁹ Overall, the pathogenesis of cases with a typical STGD1 phenotype and only one identified pathogenic *ABCA4* variant remains controversial. Nonetheless, it appears reasonable to require detection of at least one pathogenic *ABCA4* variant in patients with this distinct late-onset phenotype to assign the clinical diagnosis late-onset STGD1.

One may argue about how this distinct late-onset atrophy phenotype associated with *ABCA4* should be entitled. In the FAM Study, this phenotype was originally termed “fine granular pattern with peripheral punctate spots” (GPS[+]) and was classified as a subtype of AMD.^{11,12} In two independent approaches, we found an association of this late-onset phenotype with mono- and biallelic *ABCA4* variants.^{8,11} Here, we postulate that late-onset STGD1 and GPS[+] describe the same entity. Analyses of *ABCA4* gene variants in AMD were not performed in this study. Several earlier works have addressed the issue of *ABCA4* in large cohorts from a genetic point of view, giving controversial results.^{40–42} A recent study in AMD did not detect increased lipofuscin levels, which should be expected in retinal disease associated with *ABCA4*.⁴³ However, further contributing to this controversy will require (1) a clinically well-phenotyped AMD cohort where late-onset STGD1/GPS[+] patients are excluded, (2) a well-matched control cohort, and (3) state-of-the-art genetic approaches to identify relevant variants, which was beyond the scope of this work.

Optical coherence tomography was not included in this study, which may have caused uncertainty to the grading of foveal involvement. In particular, only the definite gradings “involved” versus “not involved” were compared in contrast to other works.^{9,44} Another limitation included the two cohorts being unequal in number of patients; because of the smaller late-onset STGD1 cohort, time-to-event curves were affected more strongly by the potential loss of follow-up here when compared with a dropout of an AMD patient. Yet time-to-event analyses are robust against such dropouts as long as patients who are more likely to suffer the event early during follow-up are not more (or less) likely to drop out. These limitations are balanced by the large cohorts of both AMD and late-onset STGD1 patients who were included into this study and followed during a long period of time.

Differential disease progression between AMD and late-onset STGD1 are particularly important to emerging therapeutic trials. Strategies in multifactorial AMD range from choroidal perfusion enhancers over neuroprotective agents to complement inhibitors.⁴ Preclinical data suggest that complement activation is a final common pathway leading to RPE cell death in both conditions^{45,46}; for AMD, the MAHALO trial also shows therapeutic effects in human.⁴⁷ Yet patients with *ABCA4*-related late-onset STGD1 will rather benefit if earlier and more specific disease processes are targeted, for example, by focusing on the visual cycle or retinal *ABCA4*-gene delivery (e.g., NCT01367444, clinicaltrials.gov and Ref. 48). Therefore, it appears prudent to carefully distinguish between late-onset STGD1 and AMD. Inclusion of late-onset STGD1 patients into interventional AMD trials, and vice versa, would blur the therapeutic effect under observation and potentially lead to a fail in proving efficacy.

Furthermore, although the clinical diagnosis of late-onset STGD1 can be supported by the detection of one disease-causing *ABCA4* variant, it would be prudent to require the

identification of two disease-causing variants before enrollment in early therapeutic trials involving late-onset STGD1 patients.

In summary, the present analysis reveals distinct progression characteristics in eyes with RPE atrophy associated with AMD and late-onset STGD1. These results underscore the relevance of refined phenotyping to predict the course of disease in a patient presenting with RPE atrophy. The results enable more sophisticated prognosis for the individual patient and should be considered when designing future interventional trials for both.

Acknowledgments

The authors thank Frans P.M. Cremers, Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands and Bernhard H.F. Weber, Institute of Human Genetics, University of Regensburg, Regensburg, Germany, for their analysis of *ABCA4* sequence variants and the collaborators of the Fundus Autofluorescence in Age-Related Macular Degeneration (FAM) Study as listed in the Appendix.

Supported by the Deutsche Forschungsgemeinschaft, Bonn, Germany, Grants FL 658/4-1 and Ho1926/3-1; BONFOR Gerok Program, Faculty of Medicine, University of Bonn, Grant O-137.0020; the Stichting A.F. Deutman Researchfonds Oogheelkunde, Nijmegen, The Netherlands; Nederlandse Oogonderzoek Stichting, Nijmegen, The Netherlands; the Stichting MaculaFonds, the Netherlands; and by the following foundations that contributed through UitZicht (Grants 2013-25 and 2014-3): Stichting Maculafonds, Landelijke Stichting voor Blinden en Slechtzienden, and Oogfonds. The funding organizations had no role in the design or conduct of this research. They provided unrestricted grants.

Disclosure: **M. Lindner**, Carl Zeiss Meditec (F, D), Genentech (F), Heidelberg Engineering (F), Optos (F), Fresenius Medical Care (I), Allergan (R), Alimera Sciences (R); **S. Lambertus**, None; **M.M. Mauschitz**, None; **N.M. Bax**, None; **E. Kersten**, None; **A. Lüning**, None; **J. Nadal**, None; **S. Schmitz-Valckenberg**, Novartis (C, F), Allergan (F), Bayer Healthcare (R, F), Carl Zeiss Meditec (F), Formycon (F), Genentech (F), Heidelberg Engineering (R, F), Optos (F); **M. Schmid**, None; **F.G. Holz**, Acucela (C, F), Alcon (C, F), Allergan (C, F), Bayer HealthCare (C, F), Carl Zeiss Meditec (F), Genentech/Roche (C, F), Heidelberg Engineering (C, F, R), Optos (F), Novartis (C, F), Boehringer Ingelheim (C), Merz (C); **C.B. Hoyng**, Bayer Healthcare (F, R), Novartis (R), Sanofi (R), Allergan (R), Roche (R), Topcon (R); **M. Fleckenstein**, Carl Zeiss Meditec (F), Genentech (R, F), Heidelberg Engineering (F, R), Optos (F), Merz (C), Bayer HealthCare (R), Novartis (R), P

References

1. Saksens NT, Fleckenstein M, Schmitz-Valckenberg S, et al. Macular dystrophies mimicking age-related macular degeneration. *Prog Retin Eye Res*. 2014;39:23–57.
2. Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. *Lancet*. 2012;379:1728–1738.
3. Schmitz-Valckenberg S, Sadda S, Staurengi G, Chew E, Fleckenstein M, Holz FG. “Geographic atrophy”: semantic considerations and literature review. *Retina*. 2016;36:2250–2264.
4. Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeren Campagne M. Geographic atrophy: clinical features and potential therapeutic approaches. *Ophthalmology*. 2014; 121:1079–1091.
5. Cideciyan AV, Swider M, Aleman TS, et al. *ABCA4* disease progression and a proposed strategy for gene therapy. *Hum Mol Genet*. 2009;18:931–941.
6. Sparrow JR, Boulton M. RPE lipofuscin and its role in retinal pathobiology. *Exp Eye Res*. 2005;80:595–606.

7. Bergmann M, Schutt F, Holz FG, Kopitz J. Inhibition of the ATP-driven proton pump in RPE lysosomes by the major lipofuscin fluorophore A2-E may contribute to the pathogenesis of age-related macular degeneration. *Faseb J*. 2004;18:562-564.
8. Westeneng-van Haaften SC, Boon CJ, Cremers FP, Hoefsloot LH, den Hollander AI, Hoyng CB. Clinical and genetic characteristics of late-onset Stargardt's disease. *Ophthalmology*. 2012;119:1199-1210.
9. Schmitz-Valckenberg S, Nadal J, Fimmers R, et al. Modeling visual acuity in geographic atrophy secondary to age-related macular degeneration. *Ophthalmologica*. 2016;235:215-224.
10. Lambertus S, Lindner M, Bax NM, et al. Progression of late-onset Stargardt disease. *Invest Ophthalmol Vis Sci*. 2016;57:5186-5191.
11. Holz FG, Bindewald-Wittich A, Fleckenstein M, et al. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. *Am J Ophthalmol*. 2007;143:463-472.
12. Fritsche LG, Fleckenstein M, Fiebig BS, et al. A subgroup of age-related macular degeneration is associated with mono-allelic sequence variants in the ABCA4 gene. *Invest Ophthalmol Vis Sci*. 2012;53:2112-2118.
13. Boon CJ, van Schooneveld MJ, den Hollander AI, et al. Mutations in the peripherin/RDS gene are an important cause of multifocal pattern dystrophy simulating STGD1/fundus flavimaculatus. *Br J Ophthalmol*. 2007;91:1504-1511.
14. Boon CJ, den Hollander AI, Hoyng CB, Cremers FP, Klevering BJ, Keunen JE. The spectrum of retinal dystrophies caused by mutations in the peripherin/RDS gene. *Prog Retin Eye Res*. 2008;27:213-235.
15. van Huet RA, Bax NM, Westeneng-Van Haaften SC, et al. Foveal sparing in Stargardt disease. *Invest Ophthalmol Vis Sci*. 2014;55:7467-7478.
16. Lange C, Feltgen N, Junker B, Schulze-Bonsel K, Bach M. Resolving the clinical acuity categories "hand motion" and "counting fingers" using the Freiburg Visual Acuity Test (FrACT). *Graefes Arch Clin Exp Ophthalmol*. 2009;247:137-142.
17. Schmitz-Valckenberg S, Brinkmann CK, Alten F, et al. Semi-automated image processing method for identification and quantification of geographic atrophy in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2011;52:7640-7646.
18. Deckert A, Schmitz-Valckenberg S, Jorzik J, Bindewald A, Holz FG, Mansmann U. Automated analysis of digital fundus autofluorescence images of geographic atrophy in advanced age-related macular degeneration using confocal scanning laser ophthalmoscopy (cSLO). *BMC Ophthalmol*. 2005;5:8.
19. Fleckenstein M, Adrion C, Schmitz-Valckenberg S, et al. Concordance of disease progression in bilateral geographic atrophy due to AMD. *Invest Ophthalmol Vis Sci*. 2010;51:637-642.
20. Lindner M, Boker A, Mauschwitz MM, et al. Directional kinetics of geographic atrophy progression in age-related macular degeneration with foveal sparing. *Ophthalmology*. 2015;122:1356-1365.
21. Feuer WJ, Yehoshua Z, Gregori G, et al. Square root transformation of geographic atrophy area measurements to eliminate dependence of growth rates on baseline lesion measurements: a reanalysis of age-related eye disease study report no. 26. *JAMA Ophthalmol*. 2013;131:110-111.
22. Fleckenstein M, Schmitz-Valckenberg S, Adrion C, et al. Tracking progression with spectral-domain optical coherence tomography in geographic atrophy caused by age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2010;51:3846-3852.
23. Dreyhaupt J, Mansmann U, Pritsch M, Dolar-Szczasny J, Bindewald A, Holz FG. Modelling the natural history of geographic atrophy in patients with age-related macular degeneration. *Ophthalmic Epidemiol*. 2005;12:353-362.
24. Turnbull BW. The empirical distribution function with arbitrary grouped, censored and truncated data. *J R Stat Soc Series B Stat Methodol*. 1976;38:290-295.
25. Schmitz-Valckenberg S, Sahel JA, Danis R, et al. Natural history of geographic atrophy progression secondary to age-related macular degeneration (Geographic Atrophy Progression Study). *Ophthalmology*. 2016;123:361-368.
26. Yehoshua Z, de Amorim Garcia Filho CA, Nunes RP, et al. Systemic complement inhibition with eculizumab for geographic atrophy in age-related macular degeneration: the COMPLETE study. *Ophthalmology*. 2014;121:693-701.
27. McBain VA, Townend J, Lois N. Progression of retinal pigment epithelial atrophy in stargardt disease. *Am J Ophthalmol*. 2012;154:146-154.
28. Chen B, Tosha C, Gorin MB, Nusinowitz S. Analysis of autofluorescent retinal images and measurement of atrophic lesion growth in Stargardt disease. *Exp Eye Res*. 2010;91:143-152.
29. Fujinami K, Sergouniotis PI, Davidson AE, et al. Clinical and molecular analysis of Stargardt disease with preserved foveal structure and function. *Am J Ophthalmol*. 2013;156:487-501.e1.
30. Sunness JS, Rubin GS, Zuckerbrod A, Applegate CA. Foveal-sparing scotomas in advanced dry age-related macular degeneration. *J Vis Impair Blind*. 2008;102:600-610.
31. de Laat P, Smeitink JA, Janssen MC, Keunen JE, Boon CJ. Mitochondrial retinal dystrophy associated with the m.3243A>G mutation. *Ophthalmology*. 2013;120:2684-2696.
32. Klevering BJ, Deutman AF, Maugeri A, Cremers FP, Hoyng CB. The spectrum of retinal phenotypes caused by mutations in the ABCA4 gene. *Graefes Arch Clin Exp Ophthalmol*. 2005;243:90-100.
33. Schmitz-Valckenberg S, Fleckenstein M, Helb HM, Charbel Issa P, Scholl HP, Holz FG. In vivo imaging of foveal sparing in geographic atrophy secondary to age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2009;50:3915-3921.
34. Fleckenstein M, Schmitz-Valckenberg S, Adrion C, et al. Progression of age-related geographic atrophy: role of the fellow eye. *Invest Ophthalmol Vis Sci*. 2011;52:6552-6557.
35. Maugeri A, van Driel MA, van de Pol DJ, et al. The 2588G→C mutation in the ABCR gene is a mild frequent founder mutation in the Western European population and allows the classification of ABCR mutations in patients with Stargardt disease. *Am J Hum Genet*. 1999;64:1024-1035.
36. Bax NM, Sangermano R, Roosing S, et al. Heterozygous deep-intronic variants and deletions in ABCA4 in persons with retinal dystrophies and one exonic ABCA4 variant. *Hum Mutat*. 2015;36:43-47.
37. Delori F, Greenberg JP, Woods RL, et al. Quantitative measurements of autofluorescence with the scanning laser ophthalmoscope. *Invest Ophthalmol Vis Sci*. 2011;52:9379-9390.
38. Duncker T, Stein GE, Lee W, et al. Quantitative fundus autofluorescence and optical coherence tomography in ABCA4 carriers. *Invest Ophthalmol Vis Sci*. 2015;56:7274-7285.
39. Muller PL, Gliem M, Mangold E, et al. Monoallelic ABCA4 mutations appear insufficient to cause retinopathy: a quantitative autofluorescence study. *Invest Ophthalmol Vis Sci*. 2015;56:8179-8186.
40. Allikmets R, Shroyer NF, Singh N, et al. Mutation of the Stargardt disease gene (ABCR) in age-related macular degeneration. *Science*. 1997;277:1805-1807.

41. Stone EM, Webster AR, Vandenberg K, et al. Allelic variation in ABCR associated with Stargardt disease but not age-related macular degeneration. *Nat Genet.* 1998;20:328-329.
42. Rivera A, White K, Stohr H, et al. A comprehensive survey of sequence variation in the ABCA4 (ABCR) gene in Stargardt disease and age-related macular degeneration. *Am J Hum Genet.* 2000;67:800-813.
43. Gliem M, Muller PL, Finger RP, McGuinness MB, Holz FG, Charbel Issa P. Quantitative fundus autofluorescence in early and intermediate age-related macular degeneration. *JAMA Ophthalmol.* 2016;134:817-824.
44. Sayegh RG, Simader C, Scheschy U, et al. A systematic comparison of spectral-domain optical coherence tomography and fundus autofluorescence in patients with geographic atrophy. *Ophthalmology.* 2011;118:1844-1851.
45. Radu RA, Hu J, Jiang Z, Bok D. Bisretinoid-mediated complement activation on retinal pigment epithelial cells is dependent on complement factor H haplotype. *J Biol Chem.* 2014;289:9113-9120.
46. Radu RA, Hu J, Yuan Q, et al. Complement system dysregulation and inflammation in the retinal pigment epithelium of a mouse model for Stargardt macular degeneration. *J Biol Chem.* 2011;286:18593-18601.
47. Roche. Lampalizumab: Potentially first treatment in geographic atrophy, an advanced form of dry AMD. *Investor Update.* Basel and London: Roche; 2013.
48. Charbel Issa P, Barnard AR, Herrmann P, Washington I, MacLaren RE. Rescue of the Stargardt phenotype in Abca4 knockout mice through inhibition of vitamin A dimerization. *Proc Natl Acad Sci U S A.* 2015;112:8415-8420.

APPENDIX

Members of the Foveal sparing Atrophy Study Team (FAST): Moritz Lindner, Stanley Lambertus, Matthias M. Mauschitz, Nathalie M. Bax, Eveline Kersten, Anna Lüning, Jennifer Nadal, Steffen Schmitz-Valckenberg, Matthias Schmid, Frank G. Holz, Carel B. Hoyng, and Monika Fleckenstein.

Members of the Fundus Autofluorescence in Age-Related Macular Degeneration (FAM) Study Group:

Department of Ophthalmology, University of Bonn, Germany: Frank G. Holz, Steffen Schmitz-Valckenberg, Monika Fleckenstein, Moritz Lindner, Julia Steinberg, Maximilian Pfau, Joanna Czauderna

Institute of Biostatistics, University of Bonn, Germany: Matthias Schmid, Rolf Fimmers, Jennifer Nadal

Department of Ophthalmology, University of Aachen, Germany: Peter Walter, Andreas Weinberger

Department of Ophthalmology, Inselspital, University of Bern, Switzerland: Sebastian Wolf, Ute Wolf-Schnurrbusch

Department of Ophthalmology, University of Heidelberg, Germany: Hans E. Völcker, Friederike Mackensen

Department of Ophthalmology, University of Leipzig, Germany: Peter Wiedemann, Andreas Mössner

Department of Ophthalmology, St. Franziskus Hospital Münster, Germany: Daniel Pauleikhoff, Georg Spital

Institute of Human Genetics, University of Regensburg, Germany: Bernhard H. F. Weber

Department of Ophthalmology, University of Würzburg, Germany: Claudia von Strachwitz