

Association Between Trends in Geographic Atrophy Growth and Age-related Macular Degeneration Drusen Phenotype

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BACKGROUND AND OBJECTIVE: The purpose of this study was to characterize the association between geographic atrophy (GA) growth and age-related macular degeneration (AMD) drusen phenotype.

PATIENTS AND METHODS: This retrospective cohort study included 59 eyes from 47 patients over 55 years with GA, followed for up to 5 years. Eyes with poor-quality imaging, irregular follow-up, or exudation were excluded. Based on multimodal retinal imaging, eyes were classified into three groups: Group 1 (reticular pseudodrusen [RPD]), Group 2 (large soft drusen [LSD]), and Group 3 (mixed RPD and LSD). Fundus autofluorescence (FAF) images were analyzed from baseline to 60 months. GA lesion area and growth rate were measured semi-automatically using Region-Finder (Heidelberg Engineering) and compared across groups over time.

RESULTS: The mean baseline GA area was $1.2 \pm 0.8 \text{ mm}^2$. The overall mean GA growth rate was $1.5 \pm 0.9 \text{ mm}^2/\text{year}$. Group 1 (RPD) showed the fastest progression at $2.56 \pm 1.09 \text{ mm}^2/\text{year}$, significantly higher than Group 2 (LSD, $1.02 \pm 0.80 \text{ mm}^2/\text{year}$) and Group 3 ($1.10 \pm 0.81 \text{ mm}^2/\text{year}$) ($P < .005$). No significant difference was observed between Groups 2 and 3 ($P = .28$). These differences remained consistent at months 12, 24, 36, 48, and 60.

CONCLUSION: GA progression is significantly faster in eyes with pure RPD phenotype. Mixed phenotype behaves similarly to LSD, supporting phenotype-specific monitoring and treatment strategies.

Age-related macular degeneration (AMD) is a chronic, progressive disease affecting the central retina and is one of the leading causes of visual impairment globally.¹ AMD is classified into three stages: early, intermediate, and advanced. Early and intermediate forms of AMD are characterized by retinal pigment epithelium (RPE) alterations and various types of deposits, generally referred to as drusen. Advanced AMD is categorized into two forms: neovascular (“wet”) age-related macular degeneration and geographic atrophy (“dry”). Geographic atrophy (GA) is characterized by the growth of sharply demarcated atrophic lesions in the outer retinal tissue and RPE in the macular region.²

GA pathophysiology is complex. Aging-related oxidative stress leads to RPE damage and drusen formation.³ Large soft drusen (LSD) are the most common type, whereas reticular pseudodrusen (RPD, also called subretinal drusenoid deposits) were first described by Mimoun et al.⁴ Drusen accumulation may trigger chronic inflammation contributing to GA.⁵

While anti-vascular endothelial growth factor (anti-VEGF) injections can restore vision in neovascular AMD, no equally effective treatment exists for pure GA. Recent therapies aim to slow GA progression,⁶ but their efficacy and safety remain debated, prompting investigation into patient subgroups with differing prognoses and disease mechanisms. Several approaches have been published to identify patterns and trends in the progres-

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Disclosure: EHS is a consultant for AbbVie, Bayer Schering-Pharma, Hoffmann-La-Roche, and Novartis. The remaining authors have disclosed no potential conflicts of interest, financial or otherwise.

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Submitted: December 24, 2025. Accepted: September 11, 2026. Published online: 2026.

doi: 10.3928/23258160-20260930-01

sion of GA, with the “FAM” study—demonstrating an association between fundus autofluorescence (FAF) patterns and growth rate—perhaps being the best example.⁷ Other studies have begun focusing on examining deposits and their potentially distinct patterns of evolution in geographic atrophy.^{8,9} We propose investigating the potential association between trends in GA growth and the concurrent presence of purely LSD, purely RPD, or the presence of both drusen phenotypes.

MATERIAL AND METHODS

This was a retrospective, longitudinal monocentric observational cohort study conducted at a tertiary retinal care center in France. Approval for the study was obtained from the local Institutional Review Board.

PATIENT SELECTION AND SETTINGS

Patients were eligible for analysis if they met the following criteria: men and women more than 55 years of age with geographic atrophy related to late AMD, exhibiting areas of GA ranging from 0.2 to 2.7 mm² on baseline fundus FAF images. In bilateral eligible cases, both eyes were included. Eligible patients were required to have available multimodal retinal imaging obtained at least 12 months prior to the onset of GA, enabling retrospective identification of drusen phenotype during the intermediate AMD stage. Participants were also required to have a minimum follow-up period of 36 months, with at least one visit per year including multimodal imaging (FAF, near-infrared reflectance [NIR], optical coherence tomography [OCT], and angiography). Although the initial study protocol specified a minimum follow-up duration of 36 months, given the availability of longer follow-up data in a subset of patients, analyses were extended beyond the initial 36-month time point (59 eyes) to include 48-month (33 eyes) and 60-month (20 eyes) outcomes when available. Visits typically occurred at 6 to 12 month intervals. Only patients with multimodal images covering the entire area of RPE atrophy at the posterior pole were included. Demographics and clinical features were recorded, and best-corrected visual acuity (BCVA) was measured at each visit using the standardized ETDRS visual acuity chart.

Exclusion criteria included potential confounding factors: high myopia, exudative AMD, previous intraocular treatment, suspected or confirmed genetic syndromes, poor-quality imaging, the presence of cuticular or colloid drusen, and drusenoid pigment epithelial detachments (PED) defined as ≥ 500 μ m in width.

Eyes were classified into three mutually exclusive groups based on multimodal imaging (see Phenotypic Lesions Identification section): pure RPD involved the presence of RPD identified on OCT without concomi-

tant LSD, pure LSD involved presence of LSD without evidence of RPD, and mixed phenotype included concurrent presence of both RPD and LSD. Eyes with isolated small drusen or drusen types not meeting criteria for either RPD or LSD were excluded from analysis.

STUDY PROTOCOL AND MULTIMODAL IMAGING

At each follow-up visit, patients underwent spectral-domain OCT using the Heidelberg Spectralis system (HRA+OCT, Heidelberg Engineering). OCT volumes covered a minimum $20^\circ \times 20^\circ$ area centered on the fovea and included 25 B-scans with 50 averaged frames, using follow-up mode when available.

FAF imaging (488-nm excitation; 500–680-nm emission; $30^\circ \times 30^\circ$) was acquired in the same session to assess GA progression, with simultaneous NIR acquisition; multicolor images were analyzed when available. Hypoautofluorescent areas on FAF were interpreted as RPE atrophy. Atrophic lesion areas were quantified on FAF by a single observer using RegionFinder software (version 1.10.2.0; Heidelberg Engineering). Subfoveal choroidal thickness was recorded at baseline and measured manually on enhanced depth imaging OCT as the perpendicular distance between Bruch’s membrane and the choroid–scleral interface.

In cases of uncertainty, atrophy was confirmed using OCT, NIR, and multicolor imaging. Foveal sparing was assessed on OCT and defined as preservation of normal foveal architecture across three consecutive B-scans. GA lesions were classified as unifocal or multifocal based on FAF.

Two experienced retinal specialists analyzed the images. If there were any disagreements, two senior retinal specialists were consulted through open adjudication.

PHENOTYPIC LESIONS IDENTIFICATION

Lesion identification was primarily based on OCT and FAF, with multimodal imaging used for confirmation when available and when necessary. Geographic atrophy was defined on FAF as sharply demarcated areas of RPE loss ≥ 175 μ m, according to the Wisconsin Grading System, and quantified using RegionFinder. On spectral-domain OCT, GA corresponded to areas ≥ 175 μ m with complete RPE loss, outer retinal thinning, and increased choroidal signal.

Large drusen were identified on OCT as dome-shaped RPE elevations ≥ 125 μ m located between the RPE basal lamina and Bruch’s membrane; a single qualifying lesion was sufficient for classification.

RPD were defined as subretinal deposits above the RPE. Based on the OCT classification by Querques et al,¹⁰ eyes were classified as having RPD when five or more distinct lesions were visible on more than one B-scan.

TABLE 1
Demographics and Clinical Features of Study Patients at Baseline

Variable	Group 1	Group 2	Group 3	P value group 1-2	P value group 1-3	P value group 2-3	All
Patients, <i>n</i>	17	15	15	–	–	–	47
Eyes, <i>n</i>	20	19	20	–	–	–	59
Female sex, <i>n</i> (%)	15 (88.2%)	11 (73.3%)	12 (80%)	.38 ^a	.65 ^a	1.0 ^a	38 (80.9%)
Mean age, (y) ± SD	77.8 ± 7.9	76.8 ± 8.0	78.8 ± 6.0	.88 ^b	.97 ^b	.92 ^b	77.8 ± 1
BCVA in logMAR ± SD (Snellen)	0.3 ± 0.3 (20/40 ± 20/40)	0.29 ± 0.2 (20/39 ± 20/32)	0.2 ± 0.1 (20/32 ± 20/25)	0.7 ^c	0.4 ^c	0.5	0.2 ± 0.1 (20/32 ± 20/25)
GA area (mm ²) ± SD	1.3 ± 0.8	1.19 ± 1.0	1.03 ± 0.7	.32 ^c	.57 ^c	.4 ^c	1.2 ± 0.8
SFCT (microns) ± SD	121 ± 58	172 ± 79	175 ± 58	.003 ^c	.001	.75 ^c	156 ± 11
Foveal sparing	17	7	7	.0008 ^b	.0008 ^b	1 ^b	31

Abbreviations: BCVA, best-corrected visual acuity; GA, Geographic atrophy measured using the RegionFinder tool on fundus autofluorescence images; logMAR, logarithm of the minimum angle of resolution (Snellen); SFCT, subfoveal choroidal thickness; y, years of age.

Group 1: Reticular pseudodrusen; Group 2: Large soft drusen; Group 3: concomitant reticular pseudodrusen and large soft drusen.

^a Fischer's exact test.

^b χ^2 test.

^c Wilcoxon test.

STATISTICAL ANALYSIS

Qualitative variables were described by numbers with percentages, and quantitative variables were described by their mean with standard deviation. Comparison between groups was performed using the Chi-square test for qualitative data and using the Wilcoxon test for quantitative data. Longitudinal data on changes in atrophy size were compared using a paired Wilcoxon test. R software (version 4.4.1) was used for statistical analysis, and $P < .05$ was retained as significant.

RESULTS

Baseline demographic and lesion characteristics, including age, sex, baseline GA area, BCVA, foveal sparing, and subfoveal choroidal thickness, are summarized in **Table 1**. Between January 1 and September 30, 2024, 549 consecutive patients with a recorded diagnosis of AMD at the tertiary center were screened by the first author. From these, 59 eyes from 47 patients (38 women and nine men) met all inclusion criteria and were included in the final analysis. Most patients were excluded due to irregular follow-up, poor-quality FAF imaging, macular exudation from conversion to neovascular AMD, or misclassification of diagnosis. A total of 17 patients (20 eyes) were classified in Group 1 (RPD), 15 patients (19 eyes) in Group 2 (large drusen), and 15 patients (20 eyes) in Group

3 (mixed phenotype). The mean age of included patients was 77.8 ± 1.0 years. Baseline BCVA was 0.2 ± 0.1 logMAR, and the mean GA lesion area was 1.2 ± 0.8 mm². The overall mean subfoveal choroidal thickness was 156 ± 11 μ m, and foveal sparing was observed in 31 eyes. No statistically significant differences were observed among groups in age, sex, baseline BCVA, or GA area. The overall GA growth rate was 1.5 ± 0.9 mm²/year over 60 months. Group-specific growth rates were: Group 1, 2.56 ± 1.09 mm²/year; Group 2, 1.02 ± 0.80 mm²/year; and Group 3, 1.10 ± 0.81 mm²/year. Rates and associated statistical comparisons are summarized in **Table 2**. Group 1 demonstrated more rapid GA growth, increasing from 2.22 ± 0.62 mm² at month 12 to 2.90 ± 1.49 mm² at month 60. Group 2 showed slower progression, from 0.54 ± 0.52 mm² to 1.18 ± 0.82 mm² over the same period. Group 3 followed a similar trajectory to Group 2, with lesion growth from 0.53 ± 0.29 mm² to 1.67 ± 1.44 mm². Growth rate of GA was statistically different between Group 1 and Groups 2 ($P < .005$) and 3 ($P < .005$) overall and at months 12, 24, 36, 48, and 60. However, no statistically significant differences were observed between Groups 2 and 3 ($P = .28$) overall or at any follow-up timepoint. Linear regression trends are illustrated in **Figure 1**, and representative FAF images from each group are shown in **Figure 2**.

TABLE 2
Rate of Progression of Geographic Atrophy

Variable	Group 1 (20 eyes)	Group 2 (20 eyes)	Group 3 (20 eyes)	P value group 1-2	P value group 1-3	P value group 2-3	All (60 eyes)
Month 12	3.50 ± 0.95 ^a (2.2 ± 0.62) ^b	1.39 ± 1.25 (0.54 ± 0.52)	1.36 ± 0.83 (0.53 ± 0.29)	.005 ^c	.005 ^c	.62 ^c	1.1 ± 0.48
Month 24	5.98 ± 1.50 (2.27 ± 1.08)	2.81 ± 2.60 (1.09 ± 0.89)	1.96 ± 0.78 (0.77 ± 0.50)	.003 ^c	.0001 ^c	.616 ^c	1.4 ± 0.82
Month 36	8.3 ± 1.7 (2.74 ± 0.84)	4.46 ± 3.21 (1.20 ± 0.86)	3.72 ± 1.85 (0.85 ± 0.68)	.002 ^c	.003 ^c	.233 ^c	1.6 ± 11.5
Month 48	11.12 ± 3.08 (2.68 ± 1.39)	5.49 ± 4.18 (1.09 ± 0.88)	6.64 ± 2.76 (1.68 ± 1.17)	.028 ^c	.004 ^c	.336 ^c	1.8 ± 1.15
Month 60	11.7 ± 4.9 (2.90 ± 1.49)	6.86 ± 5.52 (1.18 ± 0.82)	6.66 ± 2.45 (1.67 ± 1.44)	.036 ^c	.041 ^c	.606 ^c	1.9 ± 1.25
Overall	(2.56 ± 1.09)	(1.02 ± 0.80)	(1.10 ± 0.81)	>.005 ^c	>.005 ^c	.28 ^c	N/A

Abbreviation: N/A, not applicable; RPD, reticular pseudodrusen.

Group 1: RPD; group 2: large drusen; group 3: concomitant RPD and large drusen.

^a Atrophic area in square millimeters.

^b Rate of progression of geographic atrophy in square millimetre measured by region finder tool on fundus autofluorescence.

^c Paired Wilcoxon test.

DISCUSSION

Geographic atrophy represents a significant unmet medical need. The main precursor lesions of GA are the two distinct types of intermediate age-related macular degeneration (iAMD) deposits: LSD located beneath the RPE, and pseudodrusen found above the RPE. Large soft drusen are a hallmark of AMD, and disease progression is closely linked to an increasing accumulation of drusen.¹¹ Pseudodrusen have also been identified as a significant risk factor for progression to advanced AMD and as an independent factor when controlling for confounding variables such as the aforementioned LSD.^{12,13} AREDS Report No. 42 marks a major recent turning point by proposing an updated version of the simplified AREDS severity scale, incorporating reticular pseudodrusen in addition to large drusen as key risk factors, and stratifying disease progression risk according to their presence.¹⁴

Consequently, we chose to focus on these two principal lesions and classified the patients into three groups: Group 1, RPD only; Group 2, LSD only; and Group 3, mixed phenotype. Unlike Thiele et al,⁸ we excluded other types of deposits from our classification: refractile or calcified drusen, as they are late products of large soft drusen¹⁵; drusenoid PED, which results from the coalescence of LSD and represents a more advanced, heterogeneous stage not primarily associated with GA risk.¹⁶ We also excluded basal laminar drusen, also known as cuticular drusen, as, despite belonging to the spectrum of AMD, they are primarily associated with early and specific forms of the disease and should be considered separately.¹⁷

In our study, the mean overall rate of GA progression across all three groups was 1.5 ± 0.9 mm²/year, which is consistent with findings from previous research. Bassil et al¹⁸ reported a similar rate of 1.65 mm²/year in their meta-analysis (69 studies). We included patients with relatively small GA sizes with a mean baseline GA area of 1.2 ± 0.8 mm². Sunness et al¹⁹ observed that lesions greater than 1.3 mm² had a lower rate of progression compared to patients with atrophic lesions between 1.3 mm² and 8.3 mm². Our results are in agreement with this study, as the rate of progression increased over our study period and with the increasing size of the atrophic area.

Over 60 months, group 1 showed a significantly faster progression of GA compared to group 2. Our results are consistent with the literature, showing that RPD not only confers twice the risk of progressing to the late form of AMD,²⁰ but is also associated with the fastest GA enlargement.⁸

The differences in GA progression between eyes with RPD and eyes with large drusen may reflect their distinct characteristics. RPD and large drusen are both extracellular deposits with similar components, though they differ in cholesterol composition: RPD contain predominantly unesterified cholesterol, whereas large drusen contain predominantly esterified cholesterol.²¹ Additionally, RPD deposits can include inflammatory cells such as macrophages and microglia.²² Both lesion types also differ in their localization and structural characteristics. Large drusen are located beneath the RPE on its basal side, whereas RPD are subretinal deposits situated above the RPE and in contact with the photorecep-

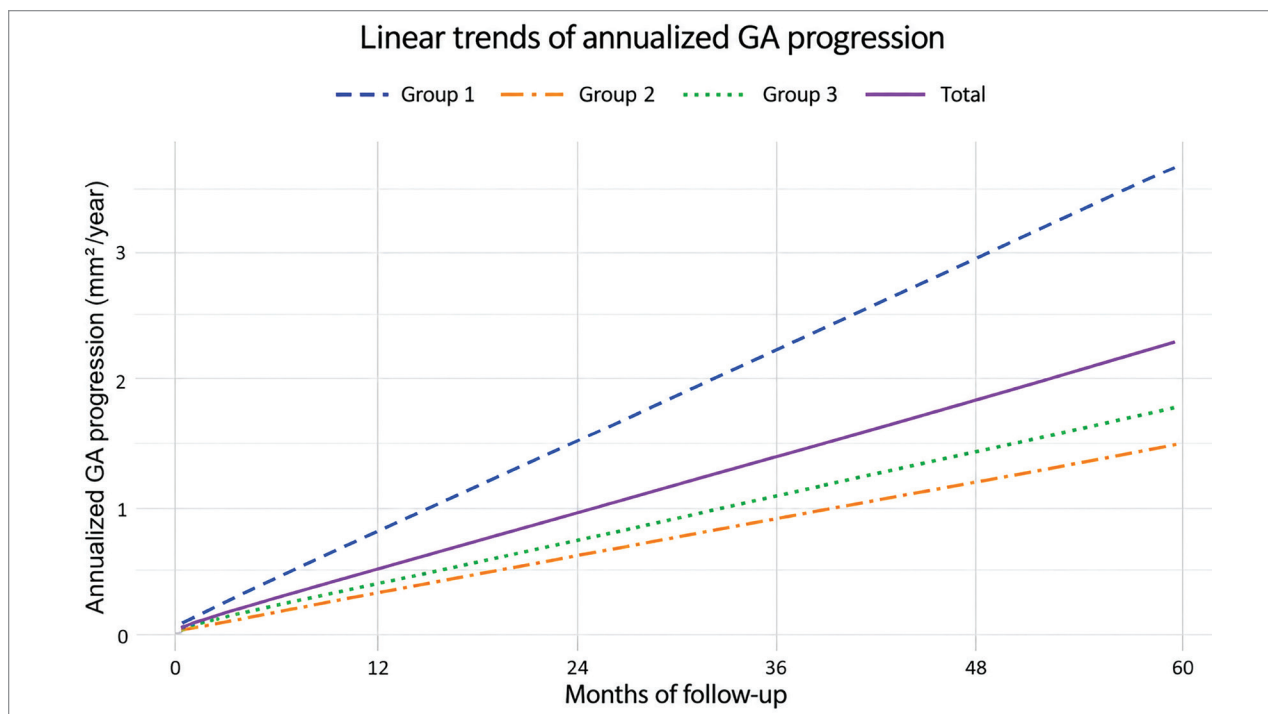


Figure 1. Geographic atrophy (GA) growth overall and by age-related macular degeneration (AMD) drusen phenotype. Linear regression analysis of GA growth from baseline to month 60. Mean growth rate was 2.56 ± 1.09 mm²/year in group 1 (reticular pseudodrusen), 1.02 ± 0.80 mm²/year in group 2 (large soft drusen), and 1.10 ± 0.81 mm²/year in group 3 (mixed phenotype). Graphs show progression for the overall cohort and each subgroup. Group 1 showed the steepest slope, indicating fastest growth; group 2 the flattest, with slower progression; and group 3 an intermediate trajectory.

tors. Large drusen can remain relatively stable for years beneath the RPE, maintaining relatively good visual function. Structural changes in the overlying RPE and outer retina can occur, sometimes followed by drusen collapse and atrophy.²³ RPD, in contrast, extend into the outer retina and through the photoreceptor layers. Greferath et al²⁴ reported that stage 3 RPD can pierce the outer limiting membrane into the outer nuclear layer, with localized photoreceptor disruption. Their study also indicated that the RPE in regions with RPD may exhibit structural abnormalities, highlighting structural differences between RPD and large drusen. Interestingly, the presence of both phenotypes showed a trend of progression similar to LSD only, thus representing a subgroup with relatively good prognosis. Fragiotta et al²⁵ recently found that large drusen at baseline appeared to have a protective effect on the expansion of GA compared to other lesions. In the case of a mixed phenotype, LSD could dominate over other lesions. This observation also supports the idea that the pure RPD phenotype may represent a distinct genetic entity, associated with a more severe clinical prognosis.

Aside from the type of deposit, previous reports showed that GA progression is complex and related to several factors, mostly baseline lesion size, subfoveal

choroidal thickness, age, genetics factors, lesion focalisation (foveal involvement), and focality (multi- or unifocal).² Out of those, our three groups did not show any differences in terms of age, sex, multifocality/unifocality, or area of GA at baseline. However, at baseline, there were differences in foveal involvement and choroidal thickness between the RPD group and the other two groups. Consistent with previous studies,²⁶ RPD eyes had thinner choroids. Current evidence does not support a direct causal role for choroidal thinning in RPD development;^{27,28} it may instead be a characteristic feature of the phenotype rather than a pathogenic mechanism. The RPD group also showed significantly more foveal sparing than the LSD and mixed groups, consistent with prior reports.²⁹ RPD preferentially affect perifoveal, rod-rich regions, whereas LSD occur in the cone-rich fovea. As these features are inherent to the RPD phenotype rather than independent confounders, groups were not matched for subfoveal choroidal thickness or foveal sparing. Although often cited, we did not analyze FAF patterns as in the FAM study,⁷ as this system relies on morphological features with variable interobserver reproducibility.³⁰

RPD presence has recently been associated with differences in treatment response in people with iAMD, suggesting that the RPD phenotype may benefit

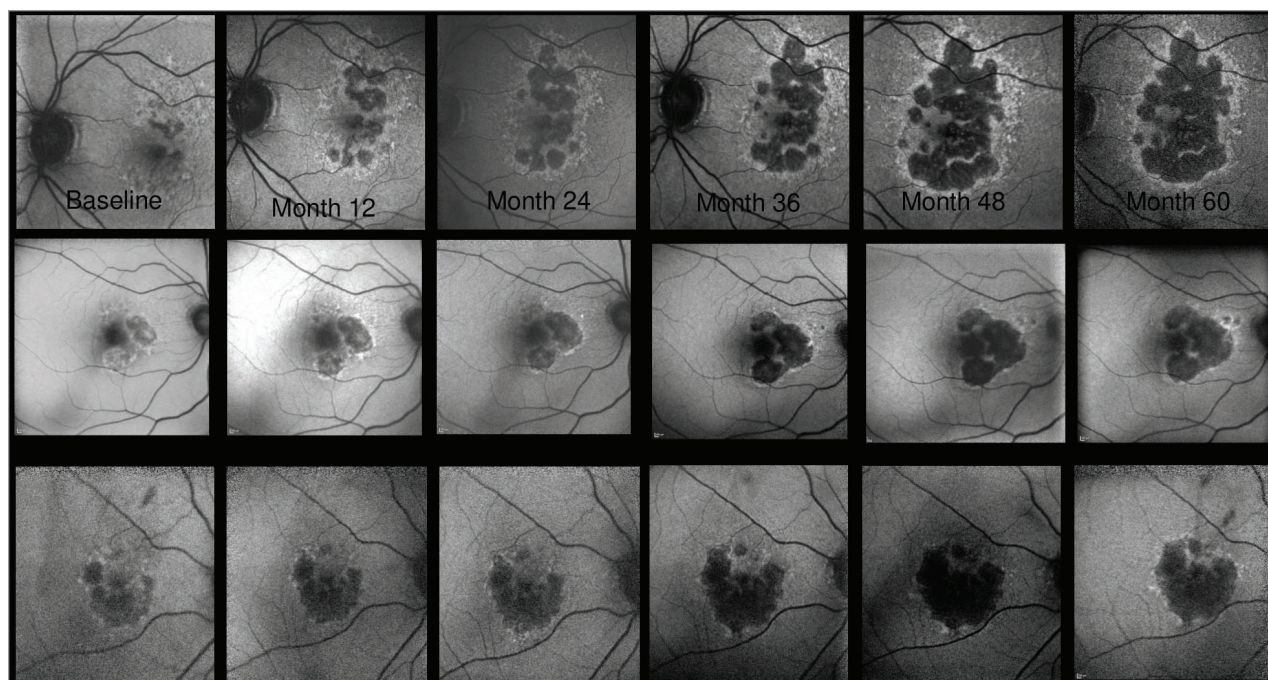


Figure 2. Fundus autofluorescence (FAF) images of representative cases showing geographic atrophy (GA) progression across age-related macular degeneration drusen phenotypes (baseline to 60 months). Top row: FAF of an 85-year-old woman. Group 1 (reticular pseudodrusen) case with GA growth from 0.97 to 11.62 mm². Middle row: FAF of a 78-year-old woman. Group 2 (large soft drusen) case with growth from 0.82 to 3.76 mm². Bottom row: FAF of a 78-year-old woman. Group 3 (mixed phenotype) case with growth from 1.2 to 4.14 mm².

from different interventions compared with eyes with only LSD.³¹

Inclusion criteria of several interventional randomized controlled trials, such as CHROMA, OAKS and DERBY, or the GATHER2 study,³² required only the presence of one to seven disk areas of total GA area, without specification of AMD drusen phenotype associated with it. Some of them, such as the CHROMA study or the BEACON study, did not reach the primary end point, whereas some others, like OAKS and DERBY or the GATHER2 study did.^{32,33} Differentiating subgroups based on AMD deposits may help to better interpret these differences.

The present study has several limitations. It is monocentric, and a relatively small sample size was included in each group due to the retrospective design and strict selection criteria, which resulted in the exclusion of a substantial number of initially screened patients. GA quantification was performed by a single grader using the RegionFinder software, without an independent review or artificial intelligence-based methods,³⁴ and only the central 30 degrees of the retina were considered, which limits generalizability. The 25-line scan protocol is relatively sparse, potentially missing some RPD or large drusen between scans. Several variables known to influence GA progression, such as smoking status, were not recorded. Despite differences between

groups, we did not match for foveal sparing or subfoveal choroidal thickness, as explained in the discussion, because these features are considered inherent characteristics of RPD rather than independent confounders. FAF patterns were not considered in our analysis due to their poor interobserver reproducibility, as discussed above. Finally, only large drusen were considered for the analyses; eyes presenting exclusively with small hard drusen (<63 µm) or medium drusen (<125 µm) were not included.

CONCLUSION

Geographic atrophy progression differs by drusen phenotype: faster with RPD, slower with LSD. When both coexist, growth resembles that of large drusen, suggesting a possible protective effect. Classifying by drusen type may guide therapy and trial design, while management currently relies on monitoring, low-vision care, and psychological support.³⁵

REFERENCES

1. Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. *Lancet*. 2012;379(9827):1728-1738. [https://doi.org/10.1016/S0140-6736\(12\)60282-7](https://doi.org/10.1016/S0140-6736(12)60282-7) PMID:22559899
2. Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular de-

- generation. *Ophthalmology*. 2018;125(3):369-390. <https://doi.org/10.1016/j.ophtha.2017.08.038> PMID:29110945
3. Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C. The pathophysiology of geographic atrophy secondary to age-related macular degeneration and the complement pathway as a therapeutic target. *Retina*. 2017;37(5):819-835. <https://doi.org/10.1097/IAE.0000000000001392> PMID:27902638
4. Mimoun G, Soubrane G, Coscas G. [Macular drusen]. *J Fr Ophthalmol*. In French. 1990;13(10):511-530. PMID:2081842
5. Bakri SJ, Bektas M, Sharp D, Luo R, Sarda SP, Khan S. Geographic atrophy: mechanism of disease, pathophysiology, and role of the complement system. *J Manag Care Spec Pharm*. 2023;29(5-a suppl):S2-S11. <https://doi.org/10.18553/jmcp.2023.29.5-a.s2> PMID:37125931
6. Khanani AM, Patel SS, Staurengi G, et al; GATHER2 trial investigators. Efficacy and safety of avacincaptad pegol in patients with geographic atrophy (GATHER2): 12-month results from a randomised, double-masked, phase 3 trial. *Lancet*. 2023;402(10411):1449-1458. [https://doi.org/10.1016/S0140-6736\(23\)01583-0](https://doi.org/10.1016/S0140-6736(23)01583-0) PMID:37696275
7. Holz FG, Bindewald-Wittich A, Fleckenstein M, Dreyhaupt J, Scholl HP, Schmitz-Valckenberg S; FAM-Study Group. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. *Am J Ophthalmol*. 2007;143(3):463-472. <https://doi.org/10.1016/j.ajo.2006.11.041> PMID:17239336
8. Thiele S, Nadal J, Pfau M, et al. Prognostic value of intermediate age-related macular degeneration phenotypes for geographic atrophy progression. *Br J Ophthalmol*. 2021;105(2):239-245. <https://doi.org/10.1136/bjophthalmol-2020-316004> PMID:32269061
9. Monés J, Biarnés M. Geographic atrophy phenotype identification by cluster analysis. *Br J Ophthalmol*. 2018;102(3):388-392. <https://doi.org/10.1136/bjophthalmol-2017-310268> PMID:28729371
10. Querques G, Canouï-Poittrine F, Coscas F, et al. Analysis of progression of reticular pseudodrusen by spectral domain-optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2012;53(3):1264-1270. <https://doi.org/10.1167/iov.11-9063> PMID:22266524
11. Lad EM, Finger RP, Guymer R. Biomarkers for the progression of intermediate age-related macular degeneration. *Ophthalmol Ther*. 2023;12(6):2917-2941. <https://doi.org/10.1007/s40123-023-00807-9> PMID:37773477
12. Zweifel SA, Imamura Y, Spaide TC, Fujiwara T, Spaide RF. Prevalence and significance of subretinal drusenoid deposits (reticular pseudodrusen) in age-related macular degeneration. *Ophthalmology*. 2010;117(9):1775-1781. <https://doi.org/10.1016/j.ophtha.2010.01.027> PMID:20472293
13. Spaide RF, Yannuzzi L, Freund KB, Mullins R, Stone E. Eyes with subretinal drusenoid deposits and no drusen: progression of macular findings. *Retina*. 2019;39(1):12-26. <https://doi.org/10.1097/IAE.0000000000002362> PMID:30312263
14. Agrón E, Domalpally A, Chen Q, Lu Z, Chew EY, Keenan TDL; AREDS and AREDS2 Research Groups. An updated simplified severity scale for age-related macular degeneration incorporating reticular pseudodrusen: Age-related Eye Disease Study Report Number 42. *Ophthalmology*. 2024;131(10):1164-1174. <https://doi.org/10.1016/j.ophtha.2024.04.011> PMID:38657840
15. Suzuki M, Curcio CA, Mullins RF, Spaide RF. REFRAC-TILE DRUSEN: Clinical imaging and candidate histology. *Retina*. 2015;35(5):859-865. <https://doi.org/10.1097/IAE.0000000000000503> PMID:25768253
16. Mrejen S, Sarraf D, Mukkamala SK, Freund KB. Multimodal imaging of pigment epithelial detachment: a guide to evaluation. *Retina*. 2013;33(9):1735-1762. <https://doi.org/10.1097/IAE.0b013e3182993f66> PMID:23873168
17. Balaratnasingam C, Cherepanoff S, Dolz-Marco R, et al. Cuticular drusen: clinical phenotypes and natural history defined using multimodal imaging. *Ophthalmology*. 2018;125(1):100-118. <https://doi.org/10.1016/j.ophtha.2017.08.033> PMID:28964580
18. Bassil FL, Colijn JM, Thiadens AAHJ, Biarnés M. Progression rate of macular retinal pigment epithelium atrophy in geographic atrophy and selected inherited retinal dystrophies. a systematic review and meta-analysis. *Am J Ophthalmol*. 2025;269:30-48. <https://doi.org/10.1016/j.ajo.2024.07.035> PMID:39153684
19. Sunness JS, Margalit E, Srikumaran D, et al. The long-term natural history of geographic atrophy from age-related macular degeneration: enlargement of atrophy and implications for interventional clinical trials. *Ophthalmology*. 2007;114(2):271-277. <https://doi.org/10.1016/j.ophtha.2006.09.016> PMID:17270676
20. Pumariega NM, Smith RT, Sohrab MA, Letien V, Souied EH. A prospective study of reticular macular disease. *Ophthalmology*. 2011;118(8):1619-1625. <https://doi.org/10.1016/j.ophtha.2011.01.029> PMID:21550118
21. Rudolf M, Malek G, Messinger JD, Clark ME, Wang L, Curcio CA. Sub-retinal drusenoid deposits in human retina: organization and composition. *Exp Eye Res*. 2008;87(5):402-408. <https://doi.org/10.1016/j.exer.2008.07.010> PMID:18721807
22. Rabiolo A, Sacconi R, Cicinelli MV, Querques L, Bandello F, Querques G. Spotlight on reticular pseudodrusen. *Clin Ophthalmol*. 2017;11:1707-1718. <https://doi.org/10.2147/OPHTH.S130165> PMID:29033536
23. Monés J, Garcia M, Biarnés M, Lakkaraju A, Ferraro L. Drusen ooze: a novel hypothesis in geographic atrophy. *Ophthalmol Retina*. 2017;1(6):461-473. <https://doi.org/10.1016/j.oret.2017.02.006> PMID:31047436
24. Greferath U, Guymer RH, Vessey KA, Brassington K, Fletcher EL. Correlation of histologic features with in vivo imaging of reticular pseudodrusen. *Ophthalmology*. 2016;123(6):1320-1331. <https://doi.org/10.1016/j.ophtha.2016.02.009> PMID:27039021
25. Fragiotta S, Dysli C, Parravano M, et al. Phenotypic characterization of predictors for development and progression of geographic atrophy using optical coherence tomography. *Retina*. 2024;44(7):1232-1241. <https://doi.org/10.1097/IAE.0000000000004090> PMID:38471039
26. Querques G, Querques L, Forte R, Massamba N, Coscas F, Souied EH. Choroidal changes associated with reticular pseudodrusen. *Invest Ophthalmol Vis Sci*. 2012;53(3):1258-1263. <https://doi.org/10.1167/iov.11-8907> PMID:22222508
27. Mrejen S, Spaide RF. The relationship between pseudodrusen and choroidal thickness. *Retina*. 2014;34(8):1560-1566. <https://doi.org/10.1097/IAE.0000000000000139> PMID:24732697
28. Vongkulsiri S, Ooto S, Mrejen S, Suzuki M, Spaide RF. The lack of concordance between subretinal drusenoid deposits and large choroidal blood vessels. *Am J Ophthalmol*. 2014;158(4):710-715. <https://doi.org/10.1016/j.ajo.2014.07.009> PMID:25034112
29. Chen L, Messinger JD, Zhang Y, Spaide RF, Freund KB, Curcio CA. Subretinal drusenoid deposit in age-related macular degeneration: histologic insights into initiation, progression to atrophy, and imaging. *Retina*. 2020;40(4):618-631. <https://doi.org/10.1097/IAE.0000000000002657> PMID:31599795
30. Biarnés M, Monés J, Trindade F, Alonso J, Arias L. Intra and interobserver agreement in the classification of fundus autofluorescence patterns in geographic atrophy secondary to age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol*. 2012;250(4):485-490. <https://doi.org/10.1007/s00417-011-1846-y> PMID:22033626
31. Guymer RH, Wu Z, Hodgson LAB, et al; Laser Intervention in Early Stages of Age-Related Macular Degeneration Study Group. Subthreshold nanosecond laser intervention in age-related macular degeneration: the LEAD Randomized Controlled Clinical Trial. *Ophthalmology*. 2019;126(6):829-838. <https://doi.org/10.1016/j.ophtha.2018.09.015> PMID:30244144
32. Heier JS, Lad EM, Holz FG, et al; OAKS and DERBY study

- investigators. Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials. *Lancet*. 2023;402(10411):1434-1448. [https://doi.org/10.1016/S0140-6736\(23\)01520-9](https://doi.org/10.1016/S0140-6736(23)01520-9) PMID:37865470
33. Freeman WR, Bandello F, Souied E, et al; BEACON Study Group. Randomized phase IIb study of brimonidine drug delivery system generation 2 for geographic atrophy in age-related macular degeneration. *Ophthalmol Retina*. 2023;7(7):573-585. <https://doi.org/10.1016/j.oret.2023.03.001> PMID:36906177
 34. Miere A, Capuano V, Kessler A, et al. Deep learning-based classification of retinal atrophy using fundus autofluorescence imaging. *Comput Biol Med*. 2021;130:104198. <https://doi.org/10.1016/j.combiomed.2020.104198> PMID:33383315
 35. Capuano V, Semoun O, Combes A, Mehanna CJ, Oubraham H, Souied EH. [Diagnostic approach and treatment paradigm in atrophic age related macular degeneration: Recommendations of the France Macula Federation]. *J Fr Ophtalmol*. 2025;48(4):104473. <https://doi.org/10.1016/j.jfo.2025.104473> PMID:40058064