# Reticular Drusen Associated with Geographic Atrophy in Age-Related Macular Degeneration

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**Purpose.** To characterize reticular drusen (RDR) in patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) in a prospective, multicenter, natural history study.

**Methods.** Confocal scanning laser ophthalmoscopy (cSLO) three-field fundus autofluorescence (FAF; exc., 488; em., 500–700 nm), near-infrared reflectance (IR; 820 nm), and blue reflectance (BR; 488 nm) images as well as red-free (RF) and color fundus (CF) camera photographs were recorded in 458 GA patients. The digital images were evaluated by two independent readers with subsequent senior reader arbitration for prevalence and topographic distribution of RDR using a modified Early Treatment Diabetic Retinopathy Study grid.

**Results.** RDR were detected with at least one cSLO modality in 286 of 458 (62%) patients in either eye (bilateral 207 [45%]) and were visible in fundus camera photographs in 66 of 371 (18%) patients (bilateral 48 [13%]). Prevalence of RDR by cSLO imaging was associated with increasing age ($P = 0.007$) and female sex ($P = 0.007$), but not with GA total lesion area ($P = 0.38$). Cohen kappa statistics showed good interobserver agreement for FAF (0.81) and IR (0.82) imaging modes, and moderate agreement was found for BR (0.48), RF (0.48), and CF (0.40). On three-field FAF images RDR were present most frequently superior to the fovea (99%).

**Conclusions.** RDR represent a common phenotypic hallmark in GA eyes. RDR are readily identified using cSLO imaging technology. These observations may explain the high prevalence determined herein, in contrast to previous reports based on fundus photographs. Incorporation of these novel imaging modalities in future natural history studies may facilitate efforts aimed at defining the role and predictive value of RDR in the progression of AMD. (ClinicalTrials.gov number, NCT00599846.) (*Invest Ophthalmol Vis Sci.* 2011;52:5009–5015) DOI:10.1167/iovs.11-7235

Among older individuals in all industrialized countries, age-related macular degeneration (AMD) is the most frequent cause of severe visual loss.[1–4] Disabling visual impairment may result from either atrophic or neovascular/exudative late-stage manifestations of the disease. Although AMD is recognized as a multifactorial complex disease with both genetic and environmental factors, the pathogenesis is still incompletely understood. Various genetic factors have recently been identified including risk variants of the ARMS2 gene and the genes encoding for proteins of the complement system.[5–10]

Clinically, focal, yellowish spots visible on ophthalmoscopy, the so-called drusen, occur in early disease stages and are regarded as a disease hallmark.[11] Histologically, drusen represent accumulation of trapped extracellular material between the retinal pigment epithelium (RPE) and Bruch's membrane.[12–14] On clinical examination drusen have been classified as hard, soft, cuticular (or basal laminar) and calcified.[15,16] Recently, reticular drusen (RDR) or reticular pseudodrusen have been recognized as an additional distinctive morphologic feature observed in AMD eyes.[17,18] The term "reticular pseudodrusen visible en lumière bleue (the pseudodrusen visible in blue light) was first used by Mimoun et al.[15] in 1990 to describe retinal lesions with a variable diameter of approximately 100 $\mu$m that did not appear hyperfluorescent on fluorescein angiography. Klein et al.[16] defined "reticular drusen" as ill-defined networks of broad, interlacing ribbons and included them in the "Wisconsin age-related maculopathy grading system." A study of the morphologic appearance of "reticular pseudodrusen" that included a histologic examination in an eye was published by Arnold and co-workers in 1995.[19] These authors described a yellowish interlacing network of oval or roundish lesions with a diameter of approximately 125–250 $\mu$m seen in red-free light by fundus photography or with the infrared wavelengths of a scanning laser ophthalmoscope. In 2002, using confocal scanning laser ophthalmoscopy fundus autofluorescence (FAF) imaging, Lois and co-workers[20] introduced in patients with early AMD the term "reticular pattern of FAF" as "ill-defined small areas of decreased FAF surrounded by areas of increased FAF." The connection of this characteristic appearance by FAF imaging to funduscopically visible RDR was described in 2005 in the report of an international workshop[21] that introduced a classification of FAF patterns in early age-related macular degeneration. Subsequently, the occurrence of RDR was also reported in patients with advanced stages of AMD.[22–25] Smith and co-workers found the incidence of retic-

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ular FAF and RDR by color fundus photography in the fellow eye of unilateral choroidal neovascularization (CNV) in 55 patients to be 36%. Cohen and co-workers[22] observed RDR in 24% of an AMD cohort ($n$ = 100) with newly diagnosed choroidal neovascularization. In a prospective, single-center study of 153 patients with different stages of AMD (131 had ≥1 eye with either geographic atrophy [GA] or CNV), Zweifel et al.[26] reported a prevalence of 8.7% using the blue channel of the color fundus camera and in 38.4% with spectral-domain optical coherence tomography (SD-OCT) imaging (data for right eyes). In the context of a genetic study, Smith and co-workers[18] reported RDR in 42 of 625 (7%) patients with grade 2 age-related maculopathy or higher. Interestingly, a total of 31 of these 42 (74%) patients had advanced AMD (GA or CNV). In the longitudinal Beaver Dam Eye study, RDR were found to confer a high risk for the progression to late-stage AMD showing even twice the risk compared with the high-risk phenotype of soft drusen and pigment changes.[24,27] In this epidemiologic study (e.g., nonspecific AMD population), the prevalence of RDR was reported to be 0.7% in individuals 43–86 years of age with an increase to 3.0% after a 15-year review period.[24]

We hypothesize that the large discrepancies in reported prevalence figures do not reflect true differences in the examined patient cohorts but are rather related to the imaging modalities used. Furthermore, we observed that RDR are more readily seen with new high-resolution imaging technology using a recently developed confocal scanning laser ophthalmoscope (cSLO). In contrast to the anatomic location of drusen material underneath the RPE, Fleckenstein et al.[28] reported that these alterations appear at the photoreceptor layer anterior to the RPE. This localization that has now been confirmed in two recent systematic analyses of AMD populations.[17,29] It has been interpreted as a clue to potential pathogenetic factors for disease damage within this anatomic layer. The aim of this study was to determine by different cSLO modalities the prevalence and topographic distribution of RDR in eyes with GA secondary to AMD, when compared with the prevalence determined by conventional fundus camera photography.

## Methods

### Population

Subjects were recruited from the natural history of Geographic Atrophy Progression (GAP) study. This prospective, multicenter, noninterventional, observational study with no masking or randomization was originally designed to identify risk factors and to quantify atrophic lesion growth in patients with GA secondary to AMD. Clinical centers in the United States, Europe, Israel, and Australia participated in this endeavor. The study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committees. Informed consent was obtained from each subject after explanation of the nature and possible consequences of the study. The primary and secondary study objects are not the aim of the current publication and will be reported elsewhere.

For inclusion, subjects had to be 50 years of age with a well-demarcated area of GA secondary to AMD in the study eye. The total GA lesion size must had been a size of ≤17.5 $mm^2$ (ca. 7 disc areas [DAs]) with one single lesion of at least 1.25 $mm^2$ (0.5 DAs). Best-corrected visual acuity in the study eye had to be 35 or more letters. In the fellow eye, drusen ≥63 $\mu$m or GA had to be present. Patients were not eligible if any signs of CNV were observed in either eye. At the baseline visit, all subjects underwent a complete ophthalmic examination including dilated fundus examination; retinal images were collected using cSLO imaging and fundus camera photography. Eligibility was initially determined by the investigator at each participating clinical center. Imaging data were sent to a central reading center for analysis.

### Imaging Protocol

Retinal imaging and data submission were performed according to standardized reading center operating procedures. These procedures included certification of each photographer before the initiation of the study at his or her clinical site. All patients underwent cSLO retinal imaging (Heidelberg Retina Angiograph, HRA classic, HRA2, or Spectralis; Heidelberg Engineering, Heidelberg, Germany) and included acquisition of near-infrared reflectance (IR; 820 nm), blue reflectance (BR; 488 nm [HRA2 and Spectralis] or 512 nm [HRA classic]), and fundus autofluorescence (FAF; exc., 488 nm; em., 500–700 nm). Images were recorded with a minimum resolution of 512 × 512 pixels. The field of view was set at 30° × 30° and centered on the macula. For the FAF modality, two additional fields were obtained, one temporal to the macula, the other one nasal to the macula with the temporal aspect of the optic disc in the center. Furthermore, three-field color fundus (CF) photographs and three-field red-free (RF) photographs were acquired using a standard fundus camera imaging system (Field 30–40° setting, minimum resolution of 2000 × 2000 pixels) that had been approved by the reading center. Fundus camera images and cSLO images were separately uploaded by each clinical site through a secure website to an electronic database. Images were then assigned to readers who analyzed the images according to predefined grading parameters. These predefined grading parameters did not include a determination of the RDR prevalence and their topographic distribution over the posterior pole for each imaging modality. Accordingly, additional grading to evaluate RDR was conducted as described below.

### Image Grading

For the current analysis, all submitted cSLO and fundus camera data for baseline visits were retrospectively reevaluated for RDR. Additional data were collected and included demographics (age and sex), stage of AMD in both eyes, and total size of GA (if applicable). The latter had been measured on the FAF images directly after data submission in the reading center using semiautomated software as previously described.[30] Eligible patients were listed in a standard (Excel; Microsoft Inc., Redmond, WA) spreadsheet according to their study identification number. Corresponding imaging data were separately evaluated by two independent readers (FA and JSS) for definitive prevalence of RDRs in IR, BR, and FAF cSLO images and CF and RF obtained by fundus camera photography, respectively (Fig. 1). In case of any discrepancy, a third grader (SSV) was asked to arbitrate. To evaluate the FAF topographic distribution, a retinal FAF montage image was automatically calculated for each identified eye with definitive RDR. To create the montage, the "compute composite" mode of the software (Heidelberg Eye Explorer) was used to merge the three captured FAF fields. To account for the enlarged view of these composite FAF images, the previously described circular grid of the Early Treatment Diabetic Retinopathy Study Grid and The Wisconsin Age-Related Maculopathy Grading System was modified by adding a horizontal line that passed through both the foveal and optic disc center (Fig. 2). A second vertical line orthogonal to the latter was then drawn through the optic disc center as well. These modifications produced a circular grid with 17 different retinal fields.

### Definitions

For FAF imaging, RDR were defined as a regular network of uniform round or oval irregularities with a diameter ranging between 50 and 400 $\mu$m. Individual lesions were further defined as those with a decreased FAF signal surrounded by mildly increased intensities (Fig. 1C). In the IR mode, RDR were identified as a pattern-like grouping of ill-defined lesions with a decreased reflectivity. For larger lesions these images may have been accompanied by a halo-like appearance exhibiting an increased central IR signal, surrounded by decreased intensity compared with the normal background signal outside individual lesions (Fig. 1A–B). For cSLO BR imaging, RDR were defined as distinctive grouping of round or oval irregularities with an increased signal in the center (Fig. 1D). For

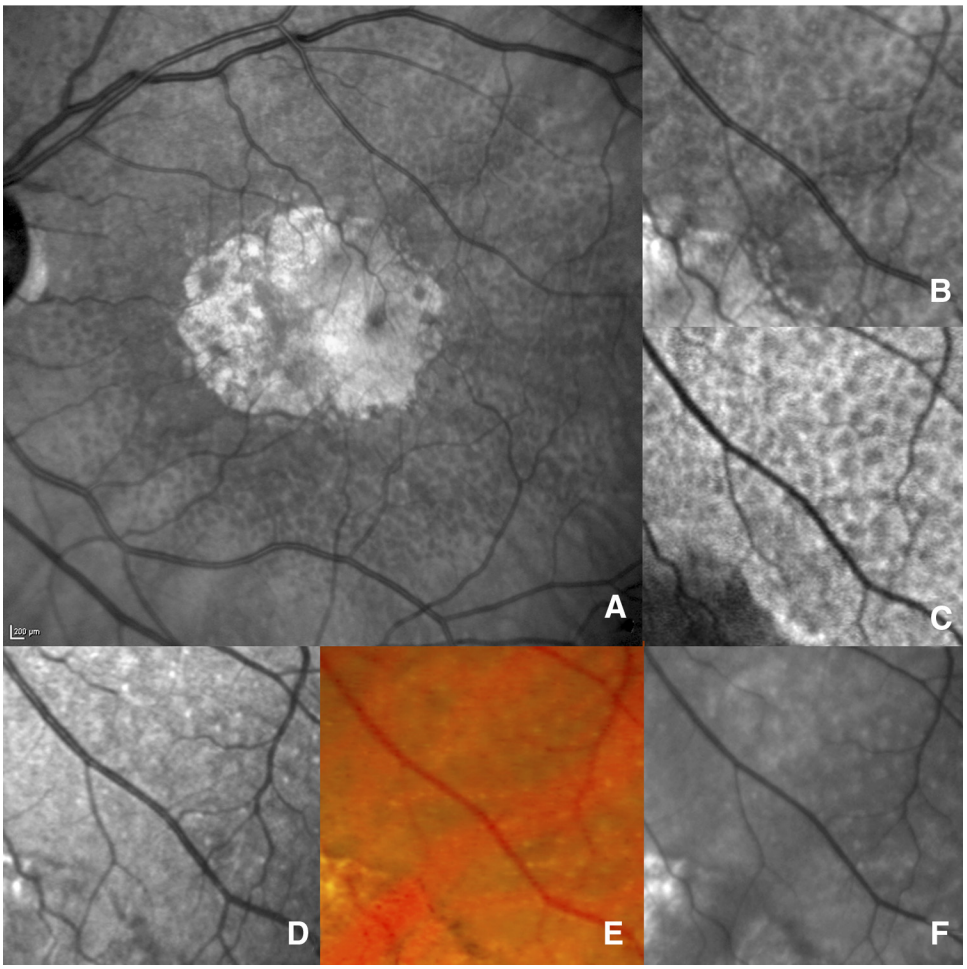


**FIGURE 1.** This representative example for a left eye of a subject with geographic atrophy secondary to AMD shows marked RDR by all imaging modalities. (**A**) Standard 30° × 30° field in the cSLO near-infrared reflectance mode. For all evaluated imaging modes, the area superior-temporal to the central atrophic patches is illustrated in a magnified window: (**B**) cSLO near-infrared reflectance; (**C**) blue autofluorescence; (**D**) blue reflectance; (**E**) color fundus camera photography; (**F**) red-free fundus camera photography.

fundus camera photographs, RDR were identified as yellow-pale (for CF; Fig. 1E) or pale (for RF; Fig. 1F) light ill-defined networks of broad, interlacing ribbons. When visible, the halo-like appearance by IR and the increased signal by BR of individual lesions hereby spatially correspond to yellow-pale dots by CF and brighter dots by RF, respectively.

## Statistical Methods

Data were compiled with a standard spreadsheet program (Microsoft Excel) and analyzed using commercially available statistical software (SAS v.9.2; SAS Institute, Cary, NC). Statistical analysis included frequency and descriptive statistics. Unweighted Cohen's $\kappa$-statistics

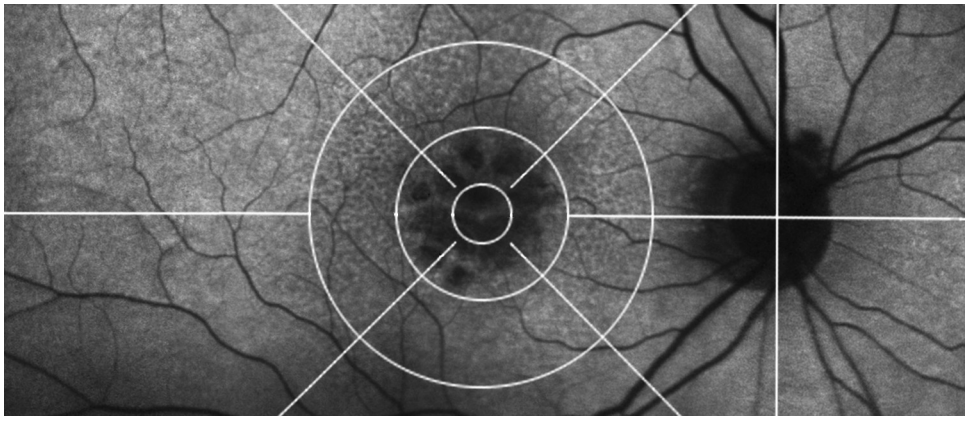

**FIGURE 2.** Illustration of the grid that was applied to determine the topographic distribution of RDR (shown for a right eye). To account for the enlarged view of the merged three-field fundus autofluorescence images, this grid was modified from the circular grid used for the evaluation of central fundus images by Klein et al.[24] The scaling is performed by assuming an optic disc diameter of 1500 $\mu$m (*black circle*), and the three diameters of the grid (*white circles*) are 1000, 3000, and 6000 $\mu$m, accordingly. The grid is centered at the fovea, the cross centered at the middle of the optic disc. This pattern results in 17 different retinal fields that were graded for RDR prevalence.

were applied to assess for interobserver reliability. If not otherwise indicated, the reported values reflect the final results after third reader arbitration. For the topographic analysis, we grouped the 17 different retinal fields in four main groups. These were (1) the center of the macula (circle with fovea in the center, diameter 3000 $\mu$m), (2) the middle of the macula (6000 $\mu$m), (3) the outer macula (beyond 6000 $\mu$m), and (4) the retina nasal to the disc. The Wilcoxon signed-rank test was used to compare the total size of atrophy with the presence of RDR. The $\chi^2$ test was applied to test for any association of the presence of RDR with sex and age. For the latter, patients were grouped in four different age groups (<70 years, 70 to 79 years, 80 to 90 years, ≥90 years). Statistical significance was set at $P < 0.05$.

## Results

A total of 607 patients with submitted cSLO data were identified; 458 of these (75%) were determined to meet the lesion-specific eligible criteria of the GAP Study. These were included in the current analysis (Fig. 3). Reasons for the 149 ineligible submissions were insufficient quality in both eyes (9%), no signs for AMD-related fundus pathology, for example, highly suspicious for retinal dystrophy (19%), signs of CNV, including fibrosis in at least one eye (36%), no single GA lesion ≥ 1.25 mm$^2$ in at least one eye (14%), total lesion size > 17.5 mm$^2$ (17%), and one subject (1%) with early AMD in one and insufficient quality to determine the AMD stage in the fellow eye. Corresponding fundus camera data were available for 371 (81%) of the 458 patients with cSLO imaging data.

### Patient Characteristics

The median age at baseline was 78.0 years (interquartile range [IQR] [73.0; 83.0]; range, 51.0–95.0 years) for the 458 included subjects. There were 184 (40%) men and 274 (60%) women. A total of 418 (91%) subjects had bilateral GA (one single GA lesion ≥ 1.25 mm$^2$ in both eyes). The median total atrophy size for all eyes was 6.5 mm$^2$ (IQR [3.18; 10.42]; range, 0.1–24.1).

### Prevalence of Reticular Drusen by Confocal Scanning Laser Ophthalmoscopy

RDR were detected in 286 of 458 (62%) subjects in at least one eye with at least one cSLO imaging modality (Fig. 3). In these 286 eyes, RDR were present in 240 (84%) right eyes, in 253 (88%) left eyes, and in both eyes of 207 subjects (72%). When assessed separately for each cSLO modality, RDR prevalence was markedly less for BR (right eyes, 25%; left eyes, 23%) when compared with IR (87% and 89%) and FAF (84% and 90%). For the analyses with each cSLO imaging modality there was moderate interobserver agreement for BR (0.48 and 0.49) and good interobserver agreement for both IR (0.82 and 0.76) and FAF (0.81 and 0.77). In most subjects (71% and 73%) RDR were observed with both IR and FAF; however, in a minority of subjects RDR were observed with only FAF (13% and 16%) or only IR (16% and 15%).

### Prevalence of Reticular Drusen by Fundus Camera Photography

RDR were detected in at least one eye of 66 of 371 (18%) subjects with at least one fundus camera photography modality. In these 66 subjects, RDR were visible in 58 (88%) right eyes, in 56 (85%) left eyes, and in both eyes of 48 (73%) subjects. There was moderate interobserver agreement for both CF (right eyes, 0.40; left eyes, 0.43) and RF (0.48; 0.42) modalities. RDR were observed with both fundus camera modalities at the same time in 66% of right and 61% of left eyes. There was a minority of subjects in which RDR were detected with only one of the two modalities (CF, 19% right eyes and 23% left eyes; RF, 16% for both eyes).

When comparing cSLO and fundus camera analyses based on the results from the 325 patients who were imaged in both eyes with all five of the different imaging modes, the presence of RDR in at least one eye was as follows: FAF 181 (55.7%), BR 58 (17.9%), IR 192 (59.1%), CF 45 (13.9%), and RF 54 (16.3%). In a post-hoc image evaluation of 100 eyes that had been graded as having RDR in all five modalities, the presence of RDR was spatially correlated between different imaging modalities, although they were better visible, and their visible extent over the posterior pole was different, being most prominent by FAF and IR cSLO imaging.

### Association with Additional Factors

For the right and left eyes with definitive RDR, based on FAF images the median total atrophy size was 6.53 mm$^2$ (IQR [3.30; 10.23]) and 6.01 mm$^2$ (IQR [3.01; 10.03]); these areas of atrophy were not significantly different from those of right and left eyes with nondetectable RDR: 6.61 mm$^2$ (IQR [3.16; 10.56]) and 7.06 mm$^2$ (IQR [3.26; 11.16]; $P = 0.38$ and 0.14). The analysis of demographic factors revealed a statistically significant association for presence of RDR with female sex ($P = 0.007$) and increasing age ($P = 0.007$) with RDR detection using cSLO imaging, but not with fundus photography ($P = 0.520$ and 0.40), respectively.

### Topographic Distribution

When the topographic RDR distribution on merged three-field FAF images was systematically analyzed (202 right eyes and 215 left eyes) RDR were most frequently located superior to the fovea in the outer macula (99.0% and 97%); the second most frequent RDR location was superio-temporal to the macula (71% and 75%) (Fig. 4). RDR occurred nasal to the optic

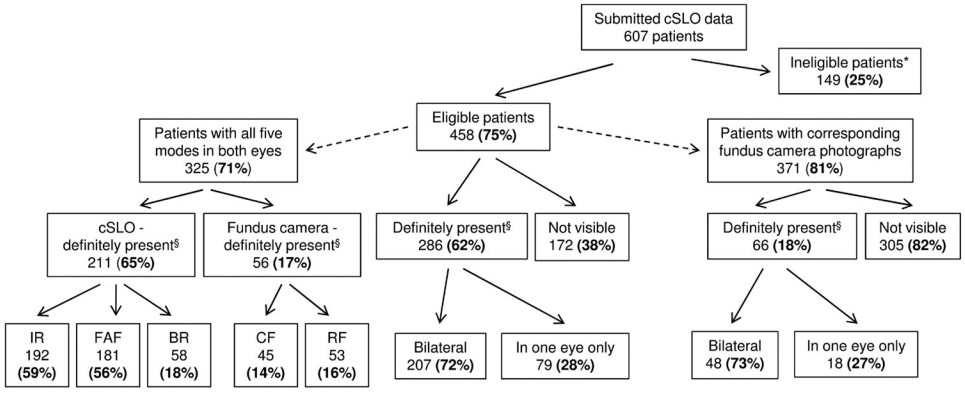


**Figure 3.** Flow diagram showing the inclusion process and the prevalence of RDR in the study population by both cSLO and fundus camera photography: *according to original study inclusion criteria; §in at least one eye and in at least one imaging modality. BR, cSLO blue reflectance; CF, color fundus camera photography; cSLO FAF, fundus autofluorescence; IR, cSLO near-infrared reflectance; RF, red-free fundus camera photography).

disc in 46% of right and 55% of left eyes, while they were never visible in the center of macula.

## Discussion

In the present report the prevalence of RDR was much higher than that previously reported. Furthermore, in this study, the prevalence was much higher on cSLO images (62%) when compared with conventional fundus photography (18%). These results suggest that RDR represent a common phenotypic biomarker in advanced atrophic AMD and that cSLO imaging is superior for detection of RDR compared with conventional fundus photography.

The identification of characteristic but subtle changes associated with RDR requires good image quality and careful analysis. It may be challenging in the majority of subjects to acquire images with even illumination and sharp focus over the entire frame. Despite good image quality, other phenotypic alterations such as soft or hard drusen may interfere with RDR detection. In the present study, using a grading system that distinguishes between definite RDR and indefinite, there was moderate to good interobserver agreement (Armstrong JR, et al. *IOVS* 2005;46:ARVO E-Abstract 220/B194). Because we are not yet able to define a clear-cut image quality threshold that permits one to exclude RDR, we consider the prevalence rate of 62% as the minimum RDR prevalence in our study cohort. Thus, RDR may be present even more frequently, but current imaging technology may limit their detection.

Given the relatively high RDR prevalence in this cohort of subjects with GA, one could speculate that RDR represent a disease hallmark. Further, their absence might reflect the presence of other diseases that mimic AMD phenotypic features. Atrophy of outer retinal layers (geographic atrophy) and associated choroidal neovascularization are obviously not specific for AMD and occur in association with various complex and monogenetic macular as well as diffuse retinal diseases. To further explore the hypothesis that RDR represent an essential disease hallmark, we have initiated a genotype-phenotype study that will assess the correlation between AMD genetic risk factors and the presence of RDR. Given both the markedly improved detection and the superior interobserver reliability compared with other imaging modalities, we believe that both IR and FAF cSLO imaging are optimal choices for the characterization of RDRs in any future AMD natural history studies.

Several recent publications have reported that en face visible RDR are spatially confined to locations that are anterior to the RPE when visualized using an instrument that simultaneously combines cSLO and SD-OCT imaging.[17,28,29] This localization suggests that RDR may play a role in disease-relevant processes at the level of the photoreceptors. In contrast, previous hypotheses on AMD pathogenesis have suggested that changes in drusen area or the location of drusen at the level of the RPE and Bruch's membrane are of predominant importance.

The histologic characterization of RDR is limited to a single case report in which the presence of RDR was related to abnormalities in the inner choroid.[19] While frequently reported with OCT imaging, characterization of RDR with OCT may be difficult; for example, it remains unclear if and to which extent the highly reflective, focal SD-OCT alterations of variable extension above the RPE are caused by optical interference. Although one might also speculate that RDR may coexist together with already well-described extracellular accumulation of material beneath the RPE as basal laminar deposits and membranous debris, the latter alterations are not yet detectable by currently imaging technology in the living human eye. The high prevalence of RDR found in the present study should in any case further prompt histopathological and biochemical studies to elucidate the exact morphologic substrate of RDR and their molecular composition.

In accordance with previous reports, we confirmed that RDR are most commonly located superior to the foveal center in the outer macula and that they are correlated with increasing age and with female sex.[19,24] The rare prevalence within 3000 $\mu$m from the foveal center in this cross-sectional study in eyes affected from late-stage atrophic AMD does not indicate that this area is an untypical location for RDR. Presence of GA is associated with the absence of RD. From this study it is not possible to address the possible presence of RD in the perifoveal area before GA developed. Using three-field FAF imaging,

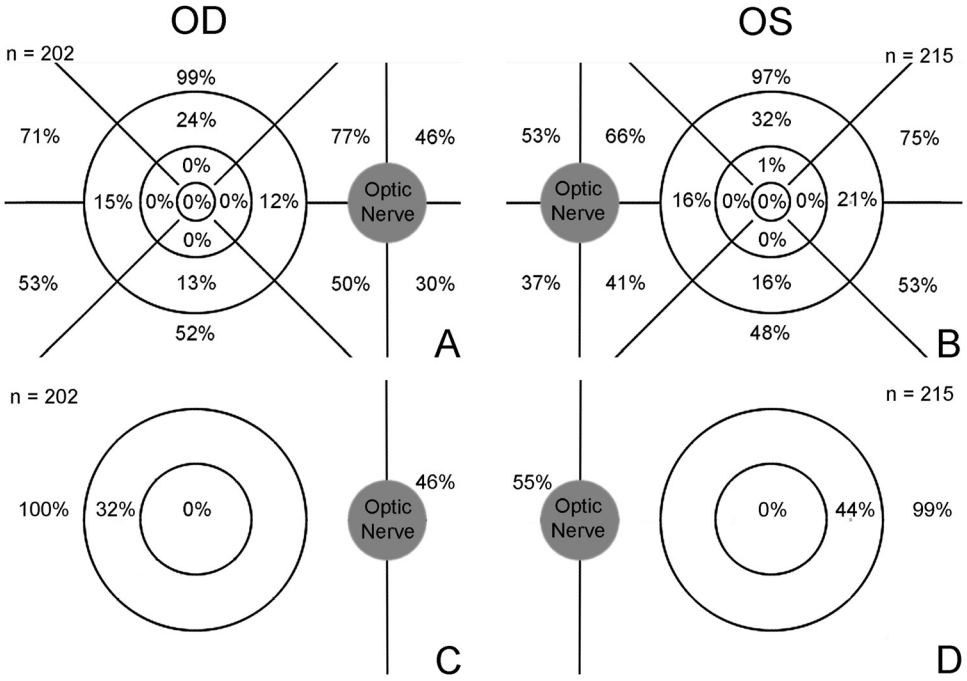


**Figure 4.** Diagrams showing the location of prevalent RDR as identified by three-field cSLO fundus autofluorescence imaging, illustrated separately for right (**A**, **C**: OD) and left eyes (**B**, **D**: OS). The *top row* shows the topographic presence for each of the 17 predefined fields (see also Fig. 2); in the *bottom row* the presence of drusen by four grouped areas is illustrated. Note that the central 3000 $\mu$m were largely involved by atrophic areas in this study population with all eyes showing patches of GA. Therefore, it cannot be excluded if RDR were present before the development of atrophy.

to the best of our knowledge, we have shown for the first time that RDR also frequently occur nasal to the optic nerve. In the context of AMD it is very uncommon for other well-described drusen variants including hard and soft drusen to occur in a nasal location. Interestingly, typical atrophic patches and Bruch's membrane elastin layer decreased thickening that develops in late-stage GA also occur nasal to the optic nerve head.[31,32] Further studies are needed to investigate if RDR may also occur beyond the retinal fields that were available in the current analysis.

Limitations of the present study include the analysis of AMD eyes that had already developed uni- or multifocal geographic atrophy. Therefore, the prevalence data would apply only to this subset of patients with AMD; similar studies with vigorous imaging protocols will be required before comparison can be made with prevalence estimates from eyes with only early-stage AMD manifestations or from eyes with neovascular late-stage manifestations. In a prospective study of patients with exudative AMD, Cohen and co-workers reported a RDR prevalence of 24%. This prevalence, which is based on color fundus photographs, is comparable to our estimate of RDR (18%) in GA patients when the prevalence was based on fundus camera photographs. It may, therefore, be speculated that RDR are not specific for advanced atrophic AMD but may occur at a similar rate in eyes with exudative AMD. Initial (unpublished) observations indicate that RDR are also commonly seen in eyes that have not already progressed to an advanced atrophic or neovascular stage. It will be of particular interest in future studies to determine the prevalence of RDR in early stage disease and the timing of their occurrence compared with "regular" drusen and pigmentary alterations, as well as the topographical spread of RDR and alterations of RDR localization over time.[22]

A further study limitation is the number of examined subjects. A total of 458 subjects were studied. Although this is a relatively high number for a prospective study with complex imaging protocols, large-scale epidemiologic studies with similar protocols may yield more accurate prevalence data and would also offer an opportunity to determine the incidence of RDR. As mentioned above, previous epidemiologic studies have used only fundus photography for analyses, which, based on the findings herein, would grossly underestimate the incidence and prevalence of RDR. Finally, given the confirmation of the post-hoc analysis, it appears to be very unlikely that the different prevalence of RDR identified by different imaging modalities would reflect different pathology rather than a differing ability to detect the same pathology.

Several reasons may be considered for the higher prevalence of RDR in this study compared with previous reports. These may include the prospective collection of imaging data according to a standardized image acquisition protocol in all patients, standardized submission of imaging data to the reading center, and certification of photographers before study initiation. Furthermore, this was a multicenter study with a relatively high number of included subjects using the latest cSLO imaging technology, which was not available at the time some of the previous studies were conducted.

In summary, the findings of this study indicate that RDR are not a rare phenotypic feature but rather a common phenotypic hallmark in eyes with GA due to AMD. In contrast to fundus photographs, RDR are readily identified in various cSLO imaging modes. This may explain the high prevalence determined herein in contrast to previous reports based on fundus photographs. Further studies are needed to explore the natural history of RDR, the potential predictive value for disease progression, and the precise morphologic and molecular substrate as well as potential genetic determinants.

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## APPENDIX

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