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# Reticular Pseudodrusen in Sorsby Fundus Dystrophy

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***Purpose:*** To investigate the association of reticular pseudodrusen (RPD) with Sorsby fundus dystrophy (SFD).

***Design:*** Prospective, monocenter, cross-sectional case series.

***Subjects:*** Sixteen patients of 4 unrelated families with SFD caused by mutations in *TIMP3*.

***Methods:*** All subjects underwent multimodal imaging including near-infrared (NIR) reflectance and fundus autofluorescence with a confocal scanning laser ophthalmoscope and spectral-domain optical coherence tomography (SD OCT).

***Main Outcome Measures:*** Prevalence, topographic distribution, and phenotype of RPD.

***Results:*** Mean age of the investigated patients was 56.8 years (range, 23−78 years). Reticular pseudodrusen were identified frequently in SFD patients in the sixth decade of life (5 of 7 [71%]) and were absent in younger (n = 3) or older (n = 6) patients. They were most abundant in the superior quadrant and spared the foveal region. Reticular pseudodrusen appeared as yellowish round to oval (dot subtype; n = 5) or confluent, wriggled (ribbon subtype; n = 3) lesions, sometimes forming irregular networks. Reticular pseudodrusen were hyporeflective on NIR reflectance and hypofluorescent on fundus autofluorescence imaging. They appeared as subretinal deposits on SD OCT imaging. Other lesions, such as peripheral pseudodrusen and soft drusen, were present less frequently.

***Conclusions:*** Reticular pseudodrusen are a frequent finding in patients with SFD. Although SFD patients with RPD are younger, distribution and phenotype of RPD are similar to those observed in patients with age-related macular degeneration. The association of RPD with SFD implicates a role of Bruch's membrane, the Bruch's membrane−retinal pigment epithelium interface, or both in the pathogenesis of RPD. *Ophthalmology 2015;122:1555-1562 © 2015 by the American Academy of Ophthalmology.*

Reticular pseudodrusen (RPD) recently have received increasing attention because of their improved visualization using novel imaging methods and because of their common association with age-related macular degeneration (AMD). Reticular pseudodrusen are considered to be an independent risk factor for progression to late forms of AMD[1−4] and may contribute to visual impairment.[5−7] Reticular pseudodrusen differ from drusen with respect to their topographic distribution at the ocular fundus and in their appearance on various imaging methods.[8−10] Histologic studies have suggested subretinal deposits internal to the retinal pigment epithelium (RPE) monolayer as the morphologic substrate of RPD,[11,12] whereas classic drusen typically are located external to the RPE.

The pathogenesis of RPD is not yet known. Several studies have indicated a contribution of choroidal changes,[13−16] and recently an association with pathologic changes of Bruch's membrane (BM) was demonstrated,[17] pointing toward a dysfunction of the choroid−BM−RPE complex. To elucidate further the pathogenesis of RPD, investigation of model diseases for primary alterations of this complex could contribute to a better understanding. Such a model disease is Sorsby fundus dystrophy (SFD), caused by mutations in the tissue inhibitor of metalloproteinases-3 (*TIMP3*) gene (Online Mendelian Inheritance in Man identifier, 136900).[18] In this rare retinal dystrophy, abnormal deposits at the interface between BM and the RPE are assumed to impair the biophysical characteristics of the choroid−BM−RPE complex with subsequent severe visual loss resulting from atrophy, secondary choroidal neovascularization (CNV), and fibrosis.[19−22]

In early disease stages, SFD is characterized by yellowish drusen-like deposits at the posterior pole.[23−26] However, a detailed characterization of these deposits with different imaging methods has not been performed to date. We investigated the phenotype, frequency, and topographic distribution of different yellowish deposits in SFD and identified RPD as the most frequently occurring lesion subtype.

## Methods

This prospective cross-sectional case series was performed between September 2013 and October 2014 at the Department of Ophthalmology of the University of Bonn, Bonn, Germany. The study adhered to the tenets of the Declaration of Helsinki. Institutional review board approval (Ethikkommission der Medizinischen Fakultät, Rheinische Friedrich-Wilhelms-Universität



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Bonn) was obtained, and written consent was obtained from each participant.

Inclusion criteria were the clinical diagnosis of SFD confirmed by DNA testing and identification of disease-causing mutations in the *TIMP3* gene as described previously.[26] All patients underwent a complete ophthalmologic examination including best-corrected visual acuity testing, funduscopy with dilated pupils, fundus photography (VISUCAM; Zeiss, Oberkochen, Germany), confocal laser scanning ophthalmoscopy, and spectral-domain optical coherence tomography (SD OCT) imaging (Spectralis HRA-OCT; Heidelberg Engineering, Heidelberg, Germany).

## Imaging Protocol and Image Analysis

The imaging protocol consisted of confocal laser scanning ophthalmoscopy imaging with 30° near-infrared (NIR) reflectance and fundus autofluorescence (488-nm excitation) images with central fixation. In selected patients, additional imaging included fluorescein angiography and indocyanine green angiography, NIR autofluorescence (787-nm excitation), and blue reflectance. Nine-field NIR reflectance imaging was performed with a 30° field of view by moving an internal fixation light through a 3×3 preset pattern. The resulting 60°×60° composite images increase the detection rate of peripheral RPD, which may be missed when restricting the captured area to 30° or when using the 55° lens of the imaging device. Spectral-domain optical coherence tomography was performed with horizontal and vertical scans with up to 100 images averaged as well as horizontal volume scans with 25°×30° field, 61 sections, and 9 images averaged centered on the fovea. If needed, localization to the foveal center was controlled manually. All confocal laser scanning ophthalmoscopy images were acquired using the high-resolution mode (1536×1536 pixels), and SD OCT images were recorded using the high-speed mode (768 A-scans per B-scan).

Images were exported from the Heidelberg Eye Explorer software (Heidelberg Engineering) and processed further using Adobe Photoshop CS5 (Adobe Systems, San Jose, CA). Image brightness and contrast were optimized by stretching the pixel histogram. Nine-field NIR reflectance images were aligned automatically and were merged using Adobe Photoshop. For evaluation of the topographic distribution of RPD, a modified Early Treatment Diabetic Retinopathy Study grid was overlaid on 9-field NIR reflectance images as described before.[17]

Based on previous reports,[2,10,27–30] RPD were defined as small round-to-oval (dot subtype) or confluent, wriggled (ribbon subtype) lesions sometimes forming a network that appear white to yellowish on funduscopy, hypofluorescent on autofluorescence, and hyporeflective on NIR reflectance imaging. On SD OCT images, RPD were defined as subretinal hyperreflective lesions associated with undulation and sometimes discontinuity of the ellipsoid band.

# Results

Sixteen patients with SFD were examined for this study. The demographic and genetic characteristics of the cohort are given in Table 1. All identified *TIMP3* mutations were reported previously as disease causing.[26,31] The mean age of the patients was 56.8±15.6 years (± standard deviation; range, 23–78 years). Nine patients were women and 7 were men.

Reticular pseudodrusen were identified in 5 of the 16 patients. Because all those with RPD were in the sixth decade of life, the frequency of RPD in this age group was 71% (5 of 7 patients; range, 52–56 years). Sorsby fundus dystrophy patients with RPD showed no late disease manifestations, such as widespread chorioretinal atrophy or subretinal fibrosis, except for 1 patient with fibrotic changes within the macular region in the fellow eye from which RPD were absent (patient 8). In 2 patients, a small CNV developed during the observational period in 1 eye and was treated successfully with intravitreal bevacizumab injections.[26] In the absence of a CNV, SFD patients with RPD reported no visual symptoms. In 2 patients (patients 5 and 7), RPD were the only notable abnormal fundus alteration. Reticular pseudodrusen usually were present bilaterally, except in 1 patient with subretinal fibrosis in the fellow eye (resulting in overall 9 eyes with RPD). All patients older than 60 years (6 of 15) had widespread chorioretinal atrophy, subretinal fibrosis, or both that did not allow reliable detection of RPD.

Phenotypically, RPD in SFD patients appeared as yellowish to whitish deposits (Fig 1A, B). Near-infrared reflectance and fundus autofluorescence imaging revealed hyporeflective or

Table 1. Demographic Data, Clinical Phenotype, and Results of Genetic Testing of Included Patients with Sorsby Fundus Dystrophy

| Patient No. | Age (yrs) | Visual Acuity | | Reticular Pseudodrusen | Peripheral Pseudodrusen | Soft Drusen | Choroidal Neovascularization | Atrophy | Mutation |
|---|---|---|---|---|---|---|---|---|---|
| | | *Right Eye* | *Left Eye* | | | | | | |
| 1 | 23 | 20/20 | 20/20 | No | No | No | No | No | p.Tyr177Cys |
| 2 | 32 | 20/20 | 20/20 | No | No | No | No | No | p.Tyr177Cys |
| 3 | 34 | 20/20 | 20/20 | No | No | No | No | No | p.Tyr177Cys |
| 4 | 51 | 20/20 | 20/20 | No | No | No | Yes | No | p.Tyr182Cys |
| 5 | 52 | 20/20 | 20/20 | Yes | No | No | No | No | p.Tyr182Cys |
| 6 | 54 | 20/20 | 20/20 | Yes | Yes | Yes | Yes | No | p.Tyr177Cys |
| 7 | 55 | 20/20 | 20/20 | Yes | No | No | No | No | p.Tyr182Cys |
| 8 | 56 | 20/50 | 20/25 | Yes | No | Yes | Yes | No | p.Glu162Lys |
| 9 | 56 | 20/60 | 20/20 | Yes | Yes | Yes | Yes | No | p.Tyr177Cys |
| 10 | 56 | HM | HM | No | No | No | Yes | Yes | p.Tyr174Cys |
| 11 | 61 | HM | 20/60 | No | Yes | No | No | Yes | p.Tyr177Cys |
| 12 | 66 | HM | HM | No | No | No | Yes | Yes | p.Tyr174Cys |
| 13 | 71 | HM | CF | No | No | No | Yes | Yes | p.Tyr182Cys |
| 14 | 75 | CF | 20/80 | No | No | No | Yes | Yes | p.Tyr177Cys |
| 15 | 77 | HM | 20/1000 | No | No | No | Yes | Yes | p.Tyr182Cys |
| 16 | 78 | HM | CF | No | No | No | Yes | Yes | p.Tyr182Cys |
| Total | | | | 5 | 3 | 2 | 10 | 7 | |

CF = counting fingers; HM = hand movements.