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Clinical and Genetic Characteristics of Japanese Patients with Age-Related Macular Degeneration and Pseudodrusen

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Purpose: To investigate differences in clinical characteristics and genotype distribution in Japanese patients with age-related macular degeneration (AMD) and pseudodrusen using multimodal imaging.

Design: Retrospective, observational case series.

Participants: A total of 101 patients (101 eyes) with AMD and pseudodrusen.

Methods: Patients underwent complete ophthalmologic examination, including color fundus photography, infrared reflectance (IR) imaging, fundus autofluorescence, confocal blue reflectance, fluorescein and indocyanine green (ICG) angiography, and spectral-domain optical coherence tomography (SD OCT). Pseudodrusen subtype was identified with multiple imaging techniques. Patients were genotyped to identify major single nucleotide polymorphisms associated with AMD (*CFH* Y402, *CFH* I62V, and *ARMS2* A69S).

Main Outcome Measures: Clinical characteristics and genetic distributions of patients with pseudodrusen.

Results: At least 1 imaging technique identified dot pseudodrusen in all 101 eyes and ribbon pseudodrusen in 53 eyes (52.5%). Forty-eight eyes (47.5%) had only dot pseudodrusen, but no eyes had only ribbon pseudodrusen or midperipheral drusen. Forty-five of 49 bilateral cases (91.8%) had the same pseudodrusen subtype in both eyes. Pseudodrusen subtype did not change during the observation period in 100 eyes (99.0%), but dot-dominant type changed to dot-ribbon type in 1 eye (1.0%). The dot and ribbon subtypes were detected in 84 (83.1%) and 51 (96.2%) eyes, respectively, using color fundus photographs. Detection sensitivity of dot pseudodrusen was high for IR (97.0%), confocal blue reflectance (95.1%), fundus autofluorescence (93.1%), and ICG (100%) imaging. Detection sensitivity for ribbon pseudodrusen was high for color fundus photography (96.2%), confocal blue reflectance (94.3%), and fundus autofluorescence (90.6%), but not for IR imaging and ICG angiography. Risk allele frequency of the *CFH* I62V polymorphism was 79.8% and 67.0% in patients with dot-dominant and dot-ribbon pseudodrusen, respectively ($P = 0.053$). The genotype frequency of *CFH* Y402H and *ARMS2* A69S polymorphisms was not significantly different between the patients with dot-dominant type and dot-ribbon type ($P = 0.647$ and $P = 0.354$, respectively).

Conclusions: Patients with pseudodrusen can be classified with dot-dominant or dot-ribbon type, and these subtypes usually are the same in both eyes. The distribution *of CFH* I62V polymorphisms may have an association with pseudodrusen subtypes. *Ophthalmology 2016;■:1–8 © 2016 by the American Academy of Ophthalmology.*

Pseudodrusen were first described by Mimoun et al[1] in 1990. They identified pseudodrusen as a distinct type of drusen that had enhanced visibility using blue light illumination. Therefore, they named it "les pseudo-drusen visible en lumiére blue (pseudodrusen best seen with blue light)." In 1991, Klein et al[2] published the Wisconsin Age-Related Maculopathy Grading System, in which they included the term "reticular drusen," a form of soft, indistinct drusen. The term "reticular" was selected because the yellowish material had a similar appearance to soft drusen, but was arranged in ill-defined networks of broad interlacing ribbons. In 1995, Arnold et al[3] combined the pseudodrusen and reticular drusen terms together to create the term "reticular pseudodrusen." They reported that two thirds of patients (n = 100) with reticular pseudodrusen had or subsequently developed choroidal neovascularization (CNV). Pseudodrusen are now recognized as a distinctive morphologic feature of age-related macular degeneration (AMD).[4–6] Evidence suggests that pseudodrusen are associated with a high risk of progression to advanced AMD and reduction in visual function.[7–14] The development of imaging methods, including scanning laser ophthalmoscopy (SLO) and optical coherence tomography (OCT), has led to additional insight into the pathogenesis of pseudodrusen.[4,10,15–26]

Suzuki et al[27] recently classified pseudodrusen into 3 categories based on appearance in color fundus photographs and infrared reflectance (IR)-SLO images. The most common type of pseudodrusen observed was "dot pseudodrusen," an orderly array of discrete dot-like

http://dx.doi.org/10.1016/j.ophtha.2016.06.052
ISSN 0161-6420/16

accumulations. A second type of pseudodrusen was observed and named "ribbon pseudodrusen" because it appeared as interlocking ribbons or bands of material. Ribbon pseudodrusen were more commonly seen in color photographs than in IR images. The third type of pseudodrusen, "midperipheral pseudodrusen," was rarely seen and appeared as small, irregularly spaced, frequently subconfluent globules. Unlike other pseudodrusen, these deposits were hyper-reflective in IR images.

Our understanding of pseudodrusen subtype characteristics is limited, especially in Asian populations. Therefore, further investigations to better understand the phenotypic and genotypic characteristics are required. The purpose of this multimodal imaging study was to investigate differences in clinical characteristics and genotypic distributions in Japanese patients with AMD and pseudodrusen. Although the term "pseudodrusen" was the first used for the lesion,[1] many other terms have been used, including "reticular pseudodrusen," "reticular drusen," "reticular macular disease," and "subretinal drusenoid deposits." In this report, we used the term "pseudodrusen" for this condition.

Methods

All study conduct adhered to the tenets of the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board and Ethics Committee of Kyoto University Graduate School of Medicine. Written informed consent was obtained from all patients who were genotyped.

Participants

We retrospectively reviewed the medical records of all patients with pseudodrusen who first visited the Macular Service at Kyoto University Hospital between July 2007 and March 2015. All included eyes had already been classified as having pseudodrusen on the basis of the presence of pseudodrusen in at least 2 imaging modalities, including color fundus photography, IR, fundus autofluorescence, confocal blue reflectance, indocyanine green (ICG) angiography, and spectral-domain (SD)-OCT imaging. The characteristic appearance of pseudodrusen in each type of imaging is described later. Subjects included in analyses had at least 1 of the following conditions in at least 1 eye: early AMD, neovascular AMD (including polypoidal choroidal vasculopathy [PCV] and retinal angiomatous proliferation [RAP]), or geographic atrophy (GA). Early AMD was defined as the presence of soft drusen ($\geq$63 μm) or areas of hyperpigmented or hypopigmented retinal pigment epithelium. An eye was diagnosed with GA when color fundus photographs showed a sharply delineated area of retinal pigment epithelium hypopigmentation, depigmentation, or apparent absence (choroidal vessels clearly visible). An eye was diagnosed with neovascular AMD when CNV was detected on fluorescein or ICG angiography and SD OCT. A diagnosis of PCV was determined on the basis of the presence of a branching vascular network that terminated in a polypoidal lesion on ICG angiography.[28] A diagnosis of RAP was given on the basis of the criteria of Yannuzzi et al,[29] which rely on fundus photography, fluorescein and ICG angiography, and SD OCT imaging. Typical AMD was defined as neovascular AMD except for PCV and RAP. To differentiate neovascular AMD from other forms of CNV, patients aged less than 50 years and eyes with high myopia (refractive error more severe than −6.00 diopters [D] or axial length >26.5 mm) were excluded. Eyes with other macular abnormalities (e.g., idiopathic CNV, trauma, uveitis, presumed ocular histoplasmosis, angioid streaks, and other secondary CNV) were excluded from analyses.

Imaging Methods

All patients underwent a complete ophthalmologic examination, including measurement of best-corrected visual acuity (BCVA) and intraocular pressure, indirect ophthalmoscopy, slit-lamp biomicroscopy (with a noncontact lens), and color fundus photography. Imaging using the following modalities also had been performed for both eyes: IR, fundus autofluorescence, confocal blue reflectance, fluorescein and ICG angiography, and SD OCT. Digital color fundus photographs (40° field) were acquired using a Topcon TRC NW6S nonmydriatic retinal camera (Topcon, Tokyo, Japan) after medical pupil dilation with phenylephrine 0.5% and tropicamide 0.5%. Fundus autofluorescence, IR, confocal blue reflectance, and ICG angiography images were acquired with a confocal SLO (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany). All IR images were obtained using an 820 nm light stimulus. Fundus autofluorescence images were obtained using a 488 nm excitation light and a barrier filter (beginning at 500 nm). Each fundus autofluorescence image was compiled by the SLO software from an average of 15 to 20 individual scans. Confocal blue reflectance images were obtained using a 488 nm light stimulus. The field of view was set to 30°×30° and was centered on the macula. All SD OCT images were obtained with the Spectralis HRA+OCT (Heidelberg Engineering). Horizontal and vertical line scans through the foveal center were obtained at a 30°angle. Next, serial horizontal scans were obtained with an examination field size of 30°×10°. At each retinal location of interest, 50 SD OCT images were acquired and averaged to reduce speckle noise.

Definitions of Pseudodrusen Subtypes

Pseudodrusen were classified into 3 categories according to the definitions proposed by Suzuki et al.[27] Dot pseudodrusen were defined as small, whitish spots on color photographs (Fig 1A). In IR (Fig 1B), autofluorescence (Fig 1D), and ICG angiography (Fig 1E) images, dot pseudodrusen appeared as hyporeflective dots or as a target appearance. In confocal blue reflectance images (Fig 1C), dot pseudodrusen appeared as discrete hyperreflective spots. Ribbon pseudodrusen were defined as an interconnected network of material that created the appearance of broad interlacing ribbons in color photographs (Fig 2A). In IR (Fig 2B), autofluorescence (Fig 2D), and ICG angiography (Fig 2E) images, ribbon pseudodrusen were characterized by a group of ill-defined, hypofluorescent interlacing lesions. In confocal blue reflectance images (Fig 1C), ribbon pseudodrusen appeared as a hyperreflective interconnected network. Midperipheral pseudodrusen were defined as small, irregularly spaced, subconfluent globules in the zone peripheral to the perifovea. In IR images, these deposits were hyper-reflective. These lesions were confirmed to be pseudodrusen on SD OCT images, appearing as subretinal accumulations of material.

The presence of each pseudodrusen subtype was independently confirmed by 2 retinal specialists (S.E. and N.U.-A.). If the diagnosis was different between graders, a senior grader (S.O.) determined the final diagnosis. Only eyes with sufficient quality images in all imaging modalities were included in analyses. If both eyes were eligible, we used only the left eye for analysis.