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Case Report

Extensive Macular Atrophy with Pseudodrusen in a Japanese Patient Evaluated by Wide-Field OCTA

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Keywords

Extensive macular atrophy with pseudodrusen · Multimodal imaging · Whole-exome sequencing · Wide-field OCTA · Age-related macular degeneration

Abstract

Extensive macular atrophy with pseudodrusen (EMAP) is a relatively newly proposed clinical entity that was first reported in 2009. Although no definitive diagnostic criteria have been defined, characteristic findings can distinguish it from other diseases, especially dry age-related macular dystrophy (AMD). Herein, we present the case of a patient with EMAP who underwent a comprehensive ophthalmic examination and whole-exome sequencing (WES). A 72-year-old Japanese man complained of progressive visual impairment in his right eye and nyctalopia. Ophthalmic examination revealed that the best-corrected visual acuity (BCVA) in decimal units was 0.08 on the right and 0.8 on the left. Fundoscopy and fundus autofluorescence (FAF) revealed well-demarcated symmetrical macular atrophy, with a vertical axis larger than the horizontal axis, which reached the vascular arcade inferiorly and exceeded it superiorly. Pseudodrusen were widespread throughout the retina in both eyes. Paving-stone degeneration was not observed in the extreme periphery of either eye. Seven months later, his left BCVA decreased to 0.3 without major changes on multimodal imaging. Based on the above findings, we diagnosed EMAP. Wide-field optical coherence tomography angiography (OCTA) showed no significant changes in the retinal vessels, but the density of choroidal vessels was reduced in the degenerated areas. We thought that this finding suggests that EMAP originates between the deep retina and choroid. WES did not reveal any candidate mutations in known pathogenic

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genes. To the best of our knowledge, this is the first report of a Japanese patient with EMAP, and no data for analysis of wide-field OCTA or equatorial OCT images of EMAP cases have been found in previous reports. EMAP is not well recognized in Asia and may be incorrectly diagnosed as dry-type AMD. EMAP should be included in the differential diagnosis of dry AMD, and this may lead to more Asians being diagnosed with EMAP in the future.

Introduction

Extensive macular atrophy with pseudodrusen (EMAP) is a rare type of macular atrophy that was first described in 2009 [1]. It is a rapidly progressive, bilateral macular degeneration with onset at a relatively young age of 40–50 years. Other characteristic findings are that macular degeneration spreads vertically rather than horizontally, resulting in a longitudinal oval shape that sometimes crosses the arcade vessels. Furthermore, pseudodrusen extends throughout the retina with paving-stone degeneration in the most peripheral retina [1]. Whether EMAP is associated with choroidal neovascularization (CNV) is controversial [1–3], and heredity has not been proven [4]. Thus, the etiology of this condition remains unclear, and there is no established treatment. Herein, we present the case of a Japanese man with EMAP with detailed ophthalmological data and genetic testing and discuss clues indicating the etiology of the disease based on wide-field optical coherence tomography angiography (OCTA) and equatorial OCT findings.

Case Presentation

A 72-year-old Japanese man was referred to our clinic with a complaint of progressive visual impairment in his right eye. He first visited an ophthalmologist approximately 6 years previously. According to the referral letter, his best-corrected visual acuity (BCVA) in decimal units at 66 years was 0.9 on the right and 1.0 on the left. Owing to the subsequent deterioration of his vision, cataract surgery was performed on both eyes at the age of 69 years. Although a short-term improvement in visual acuity was observed, his vision deteriorated further, and he was referred to our clinic. On his first visit to our clinic, he complained of vision loss in his right eye and nyctalopia in both eyes. The patient became aware of night blindness in his 50s and began having difficulty seeing, especially while driving through tunnels. He did not experience any glare or photophobia. Medical history revealed no medical conditions of note except for a squamous cell carcinoma of the fingertip that was excised at the age of 54 years. He was an internist and had no family members with similar symptoms or eye disease, and his parents were not consanguine (Fig. 1a). A detailed ophthalmological examination was performed. The BCVA was 0.08 on the right and 0.8 on the left. No special findings were observed in the anterior segment, intraocular lens, or vitreous. Intraocular pressure was 14/13 mm Hg (right eye/left eye). Fundoscopy and fundus autofluorescence (FAF) revealed well-demarcated symmetrical macular atrophy, with a vertical axis larger than the horizontal, which reached the vascular arcade inferiorly and exceeded it superiorly. Pseudodrusen were widespread throughout the retina in yellowish-white net-like patterns in both eyes (Fig. 1b–e). Wide-field fundus imaging revealed that pseudodrusen were extensively present beyond the vascular arcade. However, no obvious degeneration or low autofluorescence was observed in the mid-periphery, which is the area most likely to be

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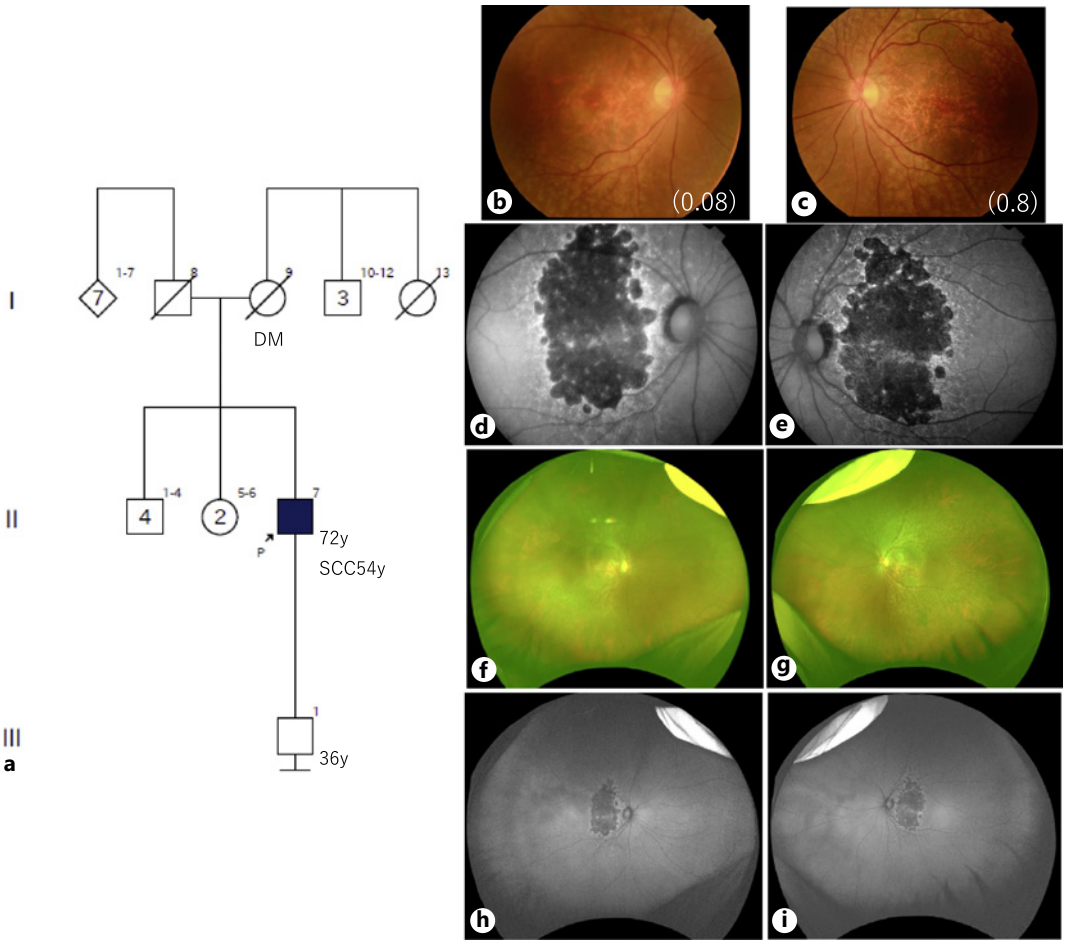

Fig. 1. a Family tree. Based on interviews with the patient, this was an isolated case. **b–i** Fundus imaging. Fundus photos (**b**, **c**) and FAF (**d**, **e**) show well-demarcated symmetrical macular atrophy, with the vertical axis larger than the horizontal, which has reached the vascular arcade inferiorly and exceeded it superiorly. UWF Fundus imaging (**f**, **g**) and UWF FAF (**h**, **i**) shows widespread pseudodrusen throughout the retina. However, no paving-stone degeneration is observed in the extreme periphery in both eyes. **b**, **d**, **f**, **h** Right eye. **c**, **e**, **g**, **i** Left eye. FAF, fundus autofluorescence; UWF, ultra-wide field.

affected first in retinitis pigmentosa (Fig. 1f–i). Paving-stone degeneration was not observed in the extreme periphery of either eye (Fig. 1f–i). Swept-source optical coherence tomography revealed extensive atrophy of the outer nuclear layer; the ellipsoid and cone outer segment termination lines could not be identified at the atrophy site and were replaced by subretinal hyperreflective material (Fig. 2a–d). There was prominent thinning of the choroid, which was consistent with a degenerative lesion (Fig. 2a–d). Fluorescein angiography (FA) showed a window defect consistent with retinal degeneration in both eyes (Fig. 2e, f); late leakage or staining was not detected (data not shown). Although choroidal vessels were clearly delineated in the degenerated area on indocyanine green angiography (IA), there was no sign of CNV (Fig. 2g, h). Wide-field OCTA showed no significant changes in the retinal vessels in the degenerated and nondegenerated areas and the superficial or deep capillary plexus (Fig. 2i–l). The size and shape of the foveal avascular zone were largely preserved (Fig. 2i–l). Focusing on the choroid, black-and-white inversion of the vessel signal was observed in the degenerated area, possibly due to atrophy of retinal pigment epithelial cells. The presence of dark areas near the vascular signals suggested that the density of choroidal vessels was reduced in the

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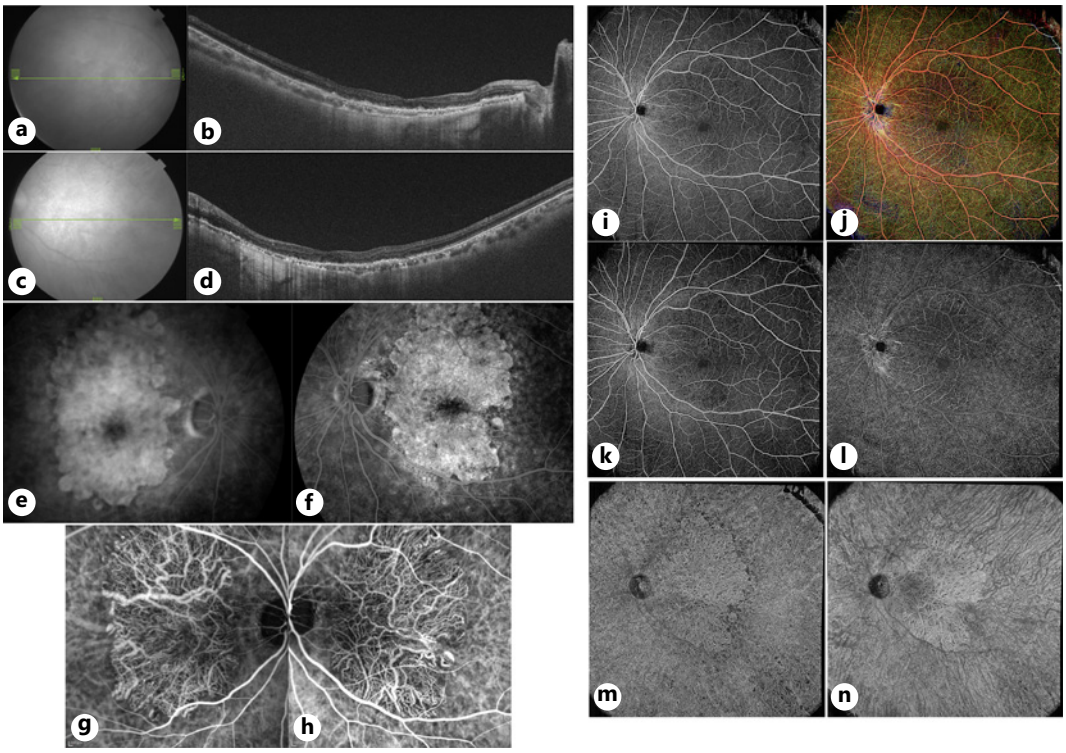

Fig. 2. a–d SSOCT images. Extensive atrophy of outer nuclear layer. The ellipsoid and COST lines are not identified at the atrophy site and are replaced by subretinal hyperreflective material. Reduction of the choroidal thickness consistent with a degenerative region is observed. **e**, **f** FA shows window defects consistent with retinal degeneration in both eyes. **g**, **h** IA shows clearly delineated choroidal vessels in the degenerated area but no sign of CNV. **i–n** OCTA montage images of the left eye. Whole retina (**i**), depth encoded (**j**), superficial (**k**), deep (**l**), choriocapillaris (**m**), choroid (**n**). **a**, **b**, **e**, **g** Right eye. **c**, **d**, **f**, **h**, **i–n** Left eye. SSOCT, swept-source optical coherence tomography; COST, cone outer segment termination; FA, fluorescein angiography; IA, indocyanine green angiography; CNV, choroidal neovascularization; OCTA, optical coherence tomography angiography.

degenerated areas (Fig. 2m, n). No suspicious signals for CNV were detected in the avascular slab (data not shown). Although kinetic and static perimetry revealed paracentral scotoma in both eyes, the position of the scotoma was unreliable because of the difficulty in central fixation. We could not confirm foveal sparing (Fig. 3a–d). The electroretinogram (ERG) waveforms were almost similar in both eyes in each measurement mode. In bright-flash ERG, although the amplitude of the a-wave was within the normal limit, the amplitude of the b-wave was slightly attenuated; we considered it an electronegative waveform (Fig. 3e). In the rod response (Fig. 3f), cone response (Fig. 3g), and 30 Hz flicker (Fig. 3h), solid waveforms were measured. In the long-flash response (Fig. 3i), both on and off responses were detected. Equatorial OCT (Fig. 3j, k) showed that pseudodrusen were located in the inner layer below the retinal pigment epithelium and partly protruded into the outer nuclear layer of the retina. From these images, we judged them to be reticular pseudodrusen [5]. The patient passed the panel D15 test with minor errors (data not shown). Anti-recovering antibody levels were below the normal threshold. We performed whole-exome sequencing (WES) and a comprehensive search for rare single-nucleotide polymorphisms in the genes responsible for hereditary retinal degeneration registered in the RetNet™ database (RetNet, https://sph.uth.edu/RetNet/). However, no candidate pathogenic mutations were identified. Seven months later, his left BCVA decreased to 0.3 without major changes on multimodal imaging. At his last

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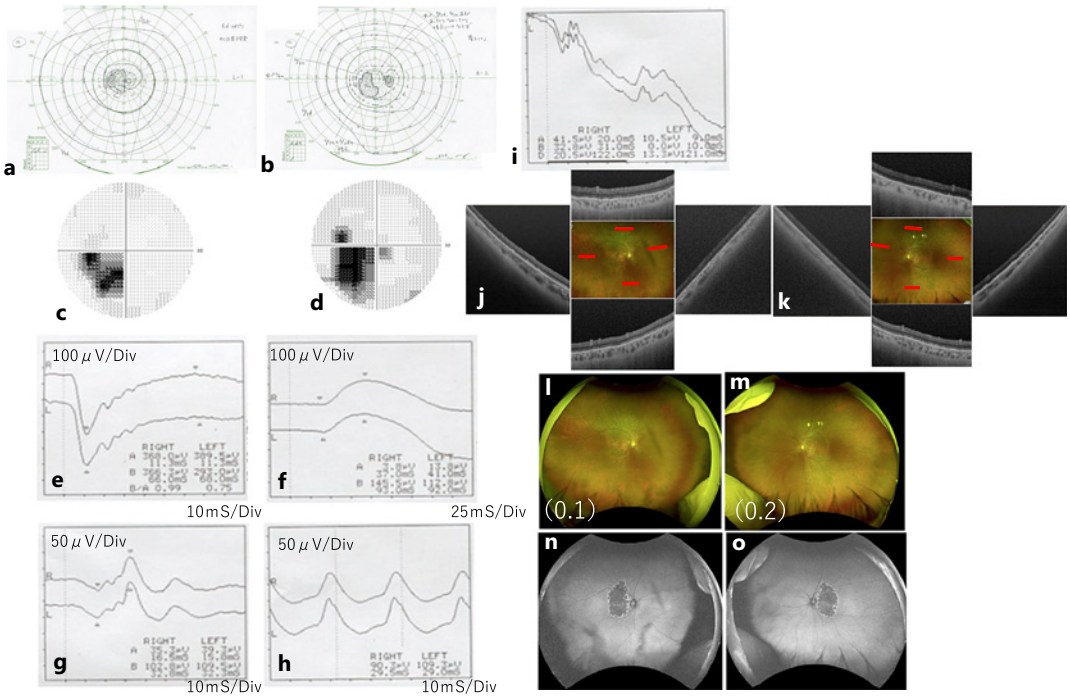

Fig. 3. Kinetic (**a**, **b**) and static (**c**, **d**) perimetry revealed paracentral scotoma in both eyes. The position of the scotoma was unreliable due to the difficulty of central fixation. **e–i** ERGs. Bright-flash (**e**), scotopic (**f**), photopic (**g**), 30 Hz flicker (**h**), long flash (**i**). Upper wave: right eye, lower wave: left eye. **j**, **k** Equatorial OCT. Red lines indicate the position of slice. UWF Fundus imaging (**l**, **m**) and UWF FAF (**n**, **o**) at the last visit. At 17 months, visual acuity in the left eye is significantly reduced, although there are no significant changes in imaging in both eyes. **b**, **d**, **j**, **l**, **n** Right eye. **a**, **c**, **k**, **m**, **o** Left eye. ERG, electroretinogram; UWF, ultra-wide field; FA, fluorescein angiography.

visit 17 months later, his BCVA was 0.1 on the right and 0.2 on the left without any sign of CNV (Fig. 3l–o).

We performed the following ophthalmologic examinations: fundus photo, FAF, and FA (TRC50DX; Topcon, Tokyo, Japan); IA (Heidelberg Spectralis; Heidelberg Engineering, Heidelberg, Germany); wide-field fundus imaging, wide-field FAF, equatorial OCT (200Tx and silver stone; Optos Inc., MA, USA); and swept-source optical coherence tomography (DRI Triton; Topcon). For ERG (LE-4000; TOMAY, Nagoya, Japan), measurements were taken after 20 min of dark adaptation, according to the instrument manual. WES was performed as described previously [6]. Briefly, DNA libraries were constructed, and 100-base pairs were amplified and paired-end sequencing of the fragments was performed on an Illumina HiSeq 2500 platform (Illumina, San Diego, CA, USA). Rare variants (minor allele frequency <0.01) were extracted from the data of the Exome Sequencing Project [7], 1000 Genomes Project [8], Human Genetic Variation Database [9], and 8.3KJPN Japan Multi Omics Reference Panel [10].

Conclusion

EMAP is a relatively newly proposed clinical entity [1], and its diagnostic criteria have not yet been established. In the original case series, EMAP has been described as having the following clinical characteristics: (1) younger age of onset (40–50 years) compared to dry age-related macular dystrophy (AMD); (2) bilateral polycyclic symmetrical extensive macular

degeneration that spreads vertically rather than horizontally, resulting in a longitudinal oval shape crossing the arcade vessels; (3) the absence of foveal sparing; (4) pseudodrusen extending throughout the retina; (5) peripheral paving-stone degeneration; (6) the absence of CNV; (7) no family history; (8) nyctalopia and/or photophobia [1]. Thereafter, two multicenter studies conducted in France with relatively large sample sizes have been published by Douillard et al. [4, 11]; these studies examined the association between clinical findings, biological factors, and dietary, environmental, and genetic risk factors in 115 patients. They reported a higher incidence of EMAP in females and that a family history of glaucoma and AMD are associated with EMAP. Furthermore, they found that Mediterranean diet reduces the incidence of EMAP, whereas areas with intensive agricultural and industrialized activities and toxic exposure during occupational activities have a higher incidence of EMAP [4, 11]. We compared the findings in our patient with the patient characteristics in the above reports to identify any consistent findings. The clinical findings were consistent except for sex, age of onset, and lack of peripheral paving-stone degeneration. WES could not detect any candidate mutations associated with inherited retinal dystrophies. Not only did the patient have no family history of AMD or glaucoma, but his work as an internist made it unlikely that he had been exposed to pesticides or other poisons for an extended time. Japanese and Mediterranean diets tend to be high in fish, which may be related not only to the late onset but also to the low incidence of EMAP among Japanese individuals and the lack of reported cases. There are reports of EMAP complicated by CNV that was treated with anti-VEGF drugs [2, 3]. In our case, although we did not detect CNV in both IA and OCTA, we believe that continued monitoring for the occurrence of CNV is a necessary precaution. OCTA is a powerful tool not only for detecting CNV but also for analyzing retinal and choroidal vessels layer-by-layer. To the best of our knowledge, only one case report of OCTA in a patient with EMAP has been published to date [12]. In that report, although the analysis was limited to the macula, a marked absence of choriocapillaris flow and mildly attenuated retinal vasculature were reported. In this report, the first wide-field OCTA imaging in EMAP is presented. In our case, although the retinal vessels were preserved, the choriocapillaris and choroidal vessels were attenuated and clearly depicted the margin of the macular atrophy lesion. This suggests a possibility that EMAP develops between the deep retina and choroid. In the future, if more cases are investigated using OCTA slab analysis, it may be possible to elucidate the etiology of EMAP. Furthermore, because wide-field OCTA images, especially those of the choriocapillaris and choroid slab, clearly depict macular atrophic lesions, OCTA slab analysis, including FAF, would be useful for follow-up of EMAP cases. Some researchers suggest that EMAP may be the same disease as dry AMD. Nyctalopia is the initial symptom of EMAP and is rarely reported in patients with dry AMD [10]. Furthermore, dry AMD is a perifoveopathy with a slow rate of progression and long-term foveal preservation [11]. EMAP shows pseudodrusen and rapid progression of macular atrophy with diffuse trickling geographic atrophy, an early and severe form of dry AMD. In contrast to EMAP, patients with diffuse trickling geographic atrophy frequently have severe vascular or cardiac disorders [11]. However, our patient had no preexisting medical conditions. Therefore, this association requires further investigation. Nyctalopia and electronegative waveform of bright-flash ERG response imply a site of retinal dysfunction occurring after phototransduction, commonly at the photoreceptor to bipolar synapse [13]. Long-flash ERG showed both on and off responses, and no candidate mutation of congenital stationary night blindness was detected by WES. We suspected that nyctalopia might be a symptom related to EMAP, as reported previously. OCT of the peripheral retina has recently become available for imaging. We used optos silver stone to analyze OCT of the equatorial region in both vertical and horizontal directions. It revealed that the peripheral pseudodrusen was also reticular pseudodrusen, and the bilateral nasal outer nuclear layer was thinning. Whether this thinning progresses to a paving-stone appearance remains to be determined and warrants careful monitoring.

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In recent years, it has become increasingly important to use multimodal imaging and carefully interpret the results for accurate diagnosis. To the best of our knowledge, this is not only the first report of a Japanese patient with EMAP but also the first analysis report of wide-field OCTA and equatorial OCT images of an EMAP case. This report implies that EMAP is found not only in Caucasians but also in Asians. Moreover, EMAP may be misdiagnosed as dry AMD. EMAP should be included in the differential diagnosis of dry AMD, and more patients will likely be diagnosed with EMAP in Asia in the future. If EMAP cases are reported in more races, it will be possible to identify racial differences in EMAP, which may lead to further elucidation of its pathogenesis.

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Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of Osaka University (approval No. 719-2, Osaka, Japan). Written informed consent was obtained from the patient for publication of details of the medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Shigeru Sato designed and conducted this study. Shigeru Sato and Sayaka Tanaka obtained informed consent, extracted DNA from the blood, and managed the samples. Takeshi Morimoto, Takashi Fujikado, Motokazu Tsujikawa, and Kohji Nishida discussed and provided useful input regarding diagnosis, follow-up, and future social support policies. Shigeru Sato drafted the manuscript, and all coauthors verified it.

Data Availability Statement

All data generated or analyzed during this study are included in this article. The data are not publicly available on legal or ethical grounds. Further inquiries can be directed to the corresponding author.

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