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Multimodal Imaging for Differential Diagnosis of Bietti Crystalline Dystrophy

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Purpose: To evaluate the diagnostic usefulness of multimodal imaging in patients with Bietti crystalline dystrophy (BCD).

Design: Retrospective cross-sectional study.

Participants: Patients with chorioretinal dystrophy accompanied by crystalline-like deposits. The right eyes of the patients were analyzed.

Methods: Fundus photograph, near-infrared reflectance (NIR), fundus autofluorescence (FAF), and OCT images were evaluated. Presence of hyperreflectivity on NIR, well-demarcated areas of decreased FAF, hyperreflective material at or on the retinal pigment epithelium–Bruch's membrane complex, and outer retinal tubulation were graded for each patient. All exons and franking introns of *CYP4V2* were screened using Sanger sequencing.

Main Outcome Measures: Sensitivity and specificity of the findings to discriminate patients with and without *CYP4V2* mutation.

Results: In total, 33 patients were included in the study. Sanger sequencing revealed homozygous or compound heterozygous *CYP4V2* mutations in 20 patients and heterozygous mutations in 2 patients. Among the investigated factors, hyperreflective appearance on NIR imaging yielded 100% sensitivity and 100% specificity in this cohort. The presence of outer retinal tubulation also was sensitive (95%), but specificity was moderate (45%). The revised diagnoses of patients without *CYP4V2* mutations included retinitis pigmentosa, late-onset macular dystrophy, and central areolar choroidal dystrophy.

Conclusions: Multimodal imaging, especially NIR imaging, is useful to differentiate BCD patients with *CYP4V2* mutations from patients with other chorioretinal dystrophies accompanied by crystalline-like retinal deposits. *Ophthalmology Retina 2018;■:1–7 © 2018 by the American Academy of Ophthalmology*

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Bietti crystalline dystrophy (BCD; Online Mendelian Inheritance in Man identifier, 210370) is a rare autosomal recessive disease characterized by the deposition of crystalline material in the retina and sometimes in the cornea.[1] *CYP4V2* was identified to be a causative gene in 2004.[2] Bietti crystalline dystrophy causes progressive chorioretinal atrophy, with associated night blindness, decreased vision, and visual field defects. Although the disease is very rare in white persons, the prevalence seems to be higher in East Asian persons because of a founder mutation.[3,4] Although the presence of crystalline materials in the posterior pole is the hallmark of BCD, they tend to disappear as the chorioretinal atrophy progresses, which makes diagnosis difficult. In addition, crystalline-like yellow or white small deposits can be seen in other diseases such as retinitis punctata albescens, drusen, fundus albipunctatus, cystinosis, and Sjögren–Larsson syndrome. Some of these cases can be differentiated by the absence of atrophy, characteristic appearance, or accompanying symptoms, but the diagnosis can be challenging depending on the stage of the disease.

Multimodal imaging of the retina is a recent trend, and detailed phenotypic descriptions have been reported for BCD. In addition to the presence of crystalline materials, the reported features include sharply demarcated areas of hypoautofluorescence, high reflectivity of crystals on near infrared reflectance (NIR) imaging, outer retinal tubulation,[5] loss of outer retinal layers, hyperreflective spots located in or on the retinal pigment epithelium (RPE)–Bruch's membrane complex, and drusen-like structures.[6,7] These features may facilitate diagnosis, although which of the findings is most relevant is unclear.

Recently, our group investigated clinical features of BCD.[7–11] During the inclusion process of these studies, we found some eyes with chorioretinal atrophy and crystalline-like deposits, but no *CYP4V2* mutations. These eyes mimicking BCD shared some features with BCD, but showed some discrepancy in the multimodal evaluations. In the present study, we explored phenotypic differences between those with and without *CYP4V2* mutations among patients with crystalline-like deposits and identify which finding is the most relevant for differential diagnosis.

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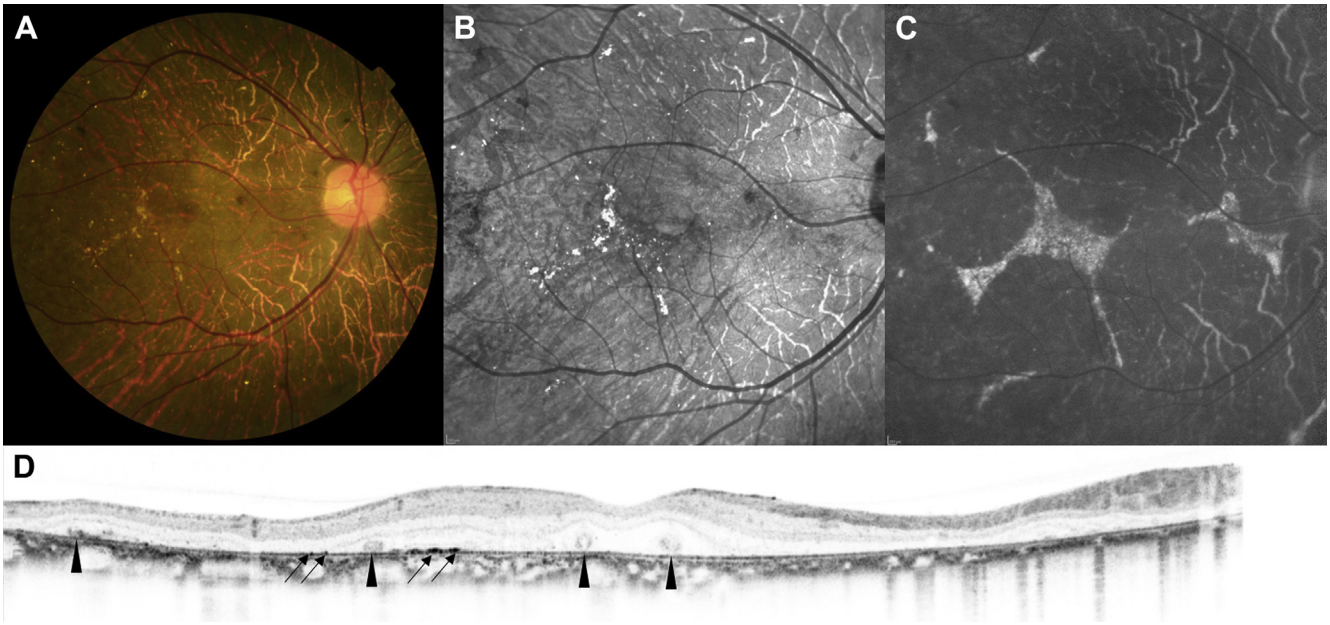

Figure 1. Fundus images of a patient with Bietti crystalline dystrophy. The patient corresponds to patient KD078 in Table S1 (available at www.ophthalmologyretina.org). **A**, Fundus photograph showing chorioretinal atrophy and glistening crystalline deposits in the macula. **B**, Near infrared reflectance image depicting the deposits more clearly. **C**, Fundus autofluorescence (FAF) image showing a well-demarcated area of decreased FAF corresponding to atrophy. Crystalline deposits did not show specific appearance in FAF. **D**, OCT image showing hyperreflectivity on or at the retinal pigment epithelium–Bruch's membrane complex (*arrows*) and outer retinal tubulations (*arrowheads*).

Methods

This retrospective, single-center, cross-sectional study was approved by the ethics committee at Kyoto University Graduate School of Medicine, Kyoto, Japan. All study protocols adhered to the tenets of the Declaration of Helsinki. All participants provided written informed consent.

Participants

Using our in-house database, we screened patients with chorioretinal dystrophy with associated crystalline-like deposits who visited our retinal degeneration service between January 2009 and September 2017. Inclusion criteria were bilateral chorioretinal atrophy and the presence of crystalline-like deposits determined using slit-lamp microscopy. Patients with unilateral lesions, a history of uveitis or other retinal diseases, or both were excluded. Family history was reviewed, but we included any inheritance trait because pseudodominance is not rare in this cohort. All patients underwent best-corrected visual acuity measurement using a Landolt C chart. OCT images, NIR images, and fundus autofluorescence (FAF) images were obtained with the Spectralis device (Heidelberg Engineering, Heidelberg, Germany). The examination protocol with OCT included a 30° cross-scan and 6 30° raster scans. Patients who were examined after 2011 also underwent ultrawide-field scanning laser ophthalmoscopy (Optos PLC, Dunfermline, United Kingdom). Electroretinography was performed according to the recommendations of the International Society for Clinical Electrophysiology of Vision published at the moment of examination (LS-C, Mayo Co, Nagoya, Japan; and Neuropack MEB-2204, Nihon Kohden, Tokyo, Japan).[12] Electroretinography was not performed in 5 patients because the patients did not want to undergo a long dark adaptation or already had undergone electroretinography at another institution. Data regarding age at onset and first symptom were extracted from clinical records.

Observation Procedures

Genetic Testing. We obtained peripheral blood from every patient and their family members when available. Genomic DNA was extracted from the leukocytes using a DNA extraction kit (QuickGene-610L; Fujifilm [Minato, Tokyo, Japan]). The quantity and quality of DNA were verified with a Nanodrop (Thermo Scientific, Waltham, MA). All 11 exons and flanking exon or intron boundaries of *CYP4V2* (NM_207352.3) were sequenced with the Sanger method using an Applied BioSystems 3130xl Genetic Analyzer (Life Technologies, Carlsbad, CA). Primers were designed using the Primer 3 program (available at http://primer3.ut.ee). The pathogenicity of a novel mutation was evaluated with the in silico prediction programs SIFT (available at http://sift.jcvi.org) and PolyPhen-2 (available at genetics.bwh.harvard.edu/pph2/).

Grading of Images. The right eye of each patient was used for grading because both eyes essentially were symmetrical. Each image was evaluated by 2 graders (A.O. and M.O.) who were blinded to the results of genetic testing. We graded presence or absence of a sharply demarcated area of decreased FAF, highly reflective materials in NIR being more evident than in fundus photographs, hyperreflective spots at the level of the RPE–Bruch's membrane complex on OCT, drusen-like deposits, and outer retinal tubulation. The grading was carried out qualitatively, that is, we did not consider the number or area of the findings. When the 2 graders disagreed, final consensus was reached through discussion.

Main Outcome Measures

The main outcome measures were sensitivity and specificity to discriminate cases with and without *CYP4V2* mutation.