1. **Title page**

**(Title)**

**Clinical and Genetic Characteristics of East Asian Patients with Occult Macular Dystrophy (Miyake’s disease); EAOMD Report No.1**

**(Authors and affiliations)**

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**Institutional Review Board:** The protocol of this study adhered to the tenets of the Declaration of Helsinki, which was approved by Institutional Review Board (IRB)/Ethics Committee. A signed informed consent was obtained from all subjects.

**2.** **Structured Abstracts**

**Purpose**: Occult macular dystrophy (OMD; MIM 613587), first described by Miyake et al. in 1989, is an inherited macular dystrophy characterized by progressive bilateral decrease of visual acuity associated with normal fundus and normal fluorescein angiograms.1 We herein describe the clinical and genetic characteristics of the cohort enrolled in the East Asian international studies of occult macular dystrophy (OMD).

**Participants and Methods**: 36 participants from 21 families with a clinical diagnosis of OMD and harboring pathogenic *RP1L1* variants (i.e. Miyake’s disease) were enrolled from 3 centers in Japan, China, and South Korea. A detailed history was obtained, and comprehensive ophthalmological examinations including spectral-domain optic coherence tomography (OCT) were performed. All detected sequence variants in the RP1L1 gene were reviewed and in silico analysis was performed including pathogenicity predictions.

**Results**: Eleven families from Japan, 6 from South Korea, 4 from China were recruited. There were 12 females and 24 males. The median age of onset was 25.5 years (range, 2-77) and the median age at the latest examination was 46.5 years (range, 13-89). The median visual acuity (VA) in the right and left eye was 0.60 (range, 0.06-1.22) and 0.60 (0.08-1.22) logarithm of the minimum angle of resolution (LogMAR) unit, respectively. A significant correlation between onset of disease and VA was revealed. The classical morphological phenotype showing both blurred ellipsoid zone and absence of interdigitation zone of the photoreceptors was demonstrated in 30 patients (83.3%), subtle photoreceptor architectural changes in 6 (16.6%). Seven pathogenic RP1L1 variants were identified, including six reported variants and one novel variants; p.R45W, p.T1194M/p.T1196I (complex), p.S1199C, p.G1200A, p.G1200D, and p.S1198F respectively. Two variants were recurrent; p.R45W (11 families, 52.4%) and p.S1199C (5 families, 23.8%). The pathogenic missense variants in 10 families (47.6%) were located in the previously reported unique motif including 6 amino acids (1196-1201).

**Conclusions**: There is a large spectrum of clinical findings in Miyake’s disease, including various onset of disease and LogMAR VA; while the characteristic photoreceptor microstructures were shared in most cases. Two hot spots including amino acid numbers 45 and 1196-1201 in the RP1L1 gene were confirmed in the East Asian population.

**3. References**

1. Miyake Y, Ichikawa K, Shiose Y, Kawase Y. Hereditary macular dystrophy without visible fundus abnormality. Am J Ophthalmol 1989;108(3):292-9.

**4. Online materials**

Figure 1. Typical clinical findings of a representative case with Miyake disease.

An image (jpg) and one figure legend (doc) are submitted separately.

Table 1. Clinical Features of 36 East Asian Patients with Occult Macular Dystrophy Harboring Pathogenic *RP1L1* Variants (Miyake Disease).

A table (doc) is submitted separately.

**5. Key words**

Occult macular dystrophy; Miyake disease; *RP1L1*; Electroretinogram; Optical coherence tomography.