論文審査の要旨及び担当者

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（論文審査の要旨）

論文題名：Spatial Functional Characteristics of East Asian Patients With Occult Macular Dystrophy (Miyake Disease); EAOMD Report No.2
（東アジア人オカルト黄斑ジストロフィ（三宅病）患者における網膜機能の空間的特徴；東アジアオカルト黄斑ジストロフィ研究レポート第2報）

This study investigated detailed functional features of occult macular dystrophy (OMD) caused by pathogenic heterozygous *RP1L1* variants (Miyake disease) based on an East Asian multicenter collaborative study. Three functional subtypes were first described based on multifocal electroretinogram (mfERG): paracentral dysfunction, homogeneous central dysfunction, and widespread dysfunction. Patients with paracentral dysfunction had the mildest phenotype, and those with homogeneous central or widespread dysfunction manifested overlapping clinical findings with severe photoreceptor changes, thereby suggesting various extents of visual impairments.

During the interview, in response to the question regarding the details of the clinical and genetic inclusion criteria, Lizhu Yang illustrated different sequencing methods used in the three centers according to the local study protocol and the process for determining the pathogenicity of the identified variants with *in silico* analyses by prediction software and databases based on the guideline of the American College of Medical Genetics. Among subjects clinically diagnosed with OMD (normal fundus with macular dysfunction), disease-causing *RP1L1* variants were identified in approximately 50%. In response to the question regarding the clinical course and mechanism of photophobia, the speculated mechanism due to the cone photoreceptor dysfunction was explained and the uncertain clinical course due to the limited follow-up term of the current study was described. In response to the questions on the affected retina layers and the pattern of morphological damages on optical coherence tomography, two predominantly affected layers of the ellipsoid zone (EZ) and the interdigitation zone (IZ) of photoreceptors in OMD were demonstrated and a pattern of IZ loss preceding to the EZ blurring was discussed; although the available data in the current cross-sectional study were not enough to conclude the last-mentioned question. In response to the question on the association between the EZ/IZ changes and the mfERG functional subtypes, local EZ changes corresponding to the functional loss were suggested, which implies further studies focusing on EZ as an important biomarker could help to monitor the disease progression. In response to the question on the affected layers in other macular dystrophies, various layers such as retinal pigment epithelium and outer nuclear layers are affected in *ABCA4*-associated and *CRX*-associated macular dystrophies were stated. In response to the question on the interpretation of each component of mfERG, further study results of latency assessment were presented, which are not in keeping with the previous studies showing the delayed mfERG latency in OMD. In response to the questions on the ethnic difference of OMD in the current study, no significant differences observed between three East Asian counties (Japan, China, and South Korea) were illustrated; however, a further study on the discovery of the ancestor of East Asian patients with *RP1L1*-associated OMD is ongoing to disclose the origin (same or different) of the study cohort in the detail. Caucasian studies had also been reported without apparent differences from the study cohort in terms of genetic characteristics, although the detailed population genetic analyses were not performed. In response to the question on the *RP1L1* function of OMD, the following hypothesis was explained: *RP1L1* encodes a component of the photoreceptor cilium and plays an important role probably in the structural and functional maintenance of the photoreceptors, as the detailed function is still uncertain due to the lack of the macula in rodent models. In response to the question on the mechanism of disease causation, a supposed hypothesis of gain of function was suggested, supported by the presence of two hot spots for missense variants in the *RP1L1* gene; albeit, further detailed studies are needed to reveal the exact mechanism. For the next step of the current report, a comparison study between *RP1L1*-associated OMD and non-*RP1L1* OMD is ongoing, which is expected to improve further delineation of the disease spectrum of OMD.

In light of the above, this study first determined a spectrum of functional phenotypes of OMD and identified the relationships between other clinical features and morphological changes, which aids in diagnosing, monitoring, and counseling patients, as well as to design future therapeutic trials. Although further studies on revealing the natural disease course and the disease-causing mechanism of the *RP1L1* gene would enrich the understanding of the disease, this paper clarified the investigation of functional features of OMD, and is approved as Lizhu Yang's dissertation.