論文審査の要旨及び担当者

報告番号	㊙甲 乙 第　　号	氏　名	藤　波　　芳

論文審査担当者　　主　査　眼科学　坪　田　一　男
ゲノム医学　小　崎　健次郎　　小児科学　長谷川　奉　延
小児科学　高　橋　孝　雄
学力確認担当者：　　審査委員長：小崎　健次郎
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（論文審査の要旨）

論文題名：Clinical and Molecular Characteristics of Childhood-Onset Stargardt Disease
（小児期発症Stargardt病における臨床像ならびに分子遺伝学的特徴）

This study addresses clinical and molecular genetic characteristics of childhood-onset Stargardt disease（STGD）and has revealed that childhood-onset STGD is characterized by more profound visual loss, early appearance of retinal morphological damages often associated with severe and extended retinal dysfunction: it is of note that, despite those characteristics, those patients with childhood-onset STGD are presented with less severe fundus abnormalities. The study has concluded that severe phenotype in childhood-onset STGD, compared to adult-onset STGD, is likely to be attributed to higher proportion of presumably null *ABCA4* variants.

In response to the question regarding the rationale for defining the childhood-onset STGD by the cutoff age of 17, the followings are presented: the cutoff line for the current study is based on the legal definition in the UK, not on the scientific background. For more appropriate cutoff age setting, the investigation in a larger worldwide cohort is currently being conducted. In response to the question regarding the validity of each of the parameters such as the onset and duration of the disease（interval between the age of onset and examination）, it was presented that all of the parameters have been validated in the studies on the natural history of STGD with more than 10 years of follow-up; 7 articles have been published. In response to the question regarding the tissue specific expression of the ABCA4 protein possibly leading to other organ/system than eyes being affected, it was presented that although no other organ has been reported to be involved in human with *ABCA4* gene mutation, the protein is expressed in mice in muscle, brain, ovary, testis and vascular tissue as well as retina. Taking into consideration the specific localization in retina of all-trans-retinal and its transportation by the ABCA4 protein, the fundamental mechanisms by which childhood-onset STGD is caused may be dysfunction of a specific cascade where a particular substrate is involved. In response to the question regarding the conservation of the ABCA4 protein in evolution and the mechanism of ABCA4 associated disease, it was presented that the conservation has been confirmed in most eukaryotes and “loss of function” is the classical concept for the pathophysiology. However, it is of note there is no functional assay available for the measurement of the direct or kinetic function of ABCA4 protein in vivo and no conclusive disease mechanism has been revealed.

Overall, this study is of scientific and social significance in the field of inherited retinal disease, delineating the clinical and genetic features of childhood-onset STGD and further investigations would enrich the work. These results also provide the crucial information in establishing a cohort of ideal candidates for clinical trials of treatment such as gene replacement therapy, regenerative cell therapy and drug treatment.