学 位 論 文 の 要 旨

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学 位 論 文 名　Analysis of LOXL1 Gene Variants in Japanese Patients with Branch Retinal Vein Occlusion

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論 文 内 容 の 要 旨

INTRODUCTION

Retinal vein occlusions (RVOs), including central retinal vein occlusion (CRVO), an occlusion at the central trunk of the retinal vein, and branch retinal vein occlusion (BRVO), an occlusion at an arteriovenous crossing where the retinal artery and vein are bound by a common adventitial sheath, are important causes of ocular morbidity. Although CRVO and BRVO have several risk factors in common, including systemic hypertension, smoking, hyperlipidemia, and elevated plasma homocysteine, they do not fully explain the involvement of the central trunk or branch of the retinal vein circulation. Exfoliation syndrome (EX), the most common identifiable cause of open-angle glaucoma worldwide, is an age-related, generalized disorder of the extracellular matrix characterized by the production and progressive accumulation of fibrillar extracellular material in many ocular tissues. A recent genome-wide association study reported that one intronic single nucleotide polymorphism (SNP; rs2165241) and two exonic SNPs (rs1048661 [R141L], rs3825942 [G153D]) in the first exon of the lysyl oxidase-like 1 (LOXL1) gene on chromosome 15q24.1 are highly associated with EX in Icelandic and Swedish populations, and that none of these SNPs was associated with primary open-angle glaucoma in the two populations. Several studies have confirmed the association of these SNPs with EX in other populations, including a Japanese population. In addition to ocular tissues, production and progressive accumulation of exfoliation materials occur in skin and various visceral organs. The association of EX with various systemic vascular and neurodegenerative disorders has been described in ischemic heart disease, carotid stiffness, cerebrovascular disease, Alzheimer disease, and hearing loss. Regarding RVO, several studies have described a possible association between

CRVO and EX diagnosed based on chart review, slit-lamp examination, histopathologic studies in enucleated eyes, and a combination of slit-lamp examination and conjunctival biopsy, while only a few studies have evaluated the association between BRVO and EX. Recently, the role of the LOXL1 polymorphism has been tested in several ocular and systemic pathologies to explore the association between EX and these pathologies, suggesting the usefulness of analyzing LOXL1 variants as a disease marker for EX. Retinal vein occlusions (RVOs), including Previous studies have described a possible association between exfoliation syndrome (EX) and various ocular and systemic vascular disorders; however, the association between EX and branch retinal vein occlusion (BRVO) remains unclear. Because slit-lamp examination may overlook latent deposits of exfoliation materials, an ocular biopsy is usually needed for a precise diagnosis. We evaluated a possible association between EX and BRVO using lysyl oxidase-like 1 (LOXL1) gene variants as alternative markers for EX. In the current study, we tested the association between LOXL1 variants and BRVO in a Japanese population to explore a possible association between EX and BRVO.

MATERIALS AND METHODS

Unrelated Japanese subjects with BRVO (n=78) were consecutively recruited at the Shimane University Hospital and Iinan Hospital in Shimane, Japan. All subjects underwent a dilated pupil examination of the anterior segments, ocular media, and fundus using a slit-lamp and a funduscope. BRVO was diagnosed if the fundus examination revealed venous dilation and tortuosity with flame-shaped and dot-blot hemorrhages in a wedge-shaped region. The BRVO group was divided into two subgroups based on the presence (EX+, n=11) or absence (EX-, n=67) of clinically detectable ocular deposits of exfoliation material. Deposits of exfoliation material were identified if the slit-lamp examination revealed a typical pattern of exfoliation material on the anterior lens surface and/or pupillary margin. The data set from patients with cataract without deposits of exfoliation material (CT, n=158) reported in our previous study served as a control. Genomic DNA was extracted from the peripheral white blood cells of each subject. A polymerase chain reaction was performed using primers designed to amplify the genomic region containing both rs1048661 and rs3825942 or only rs2165241. The sequence was determined based on the dideoxy terminator method. The study protocol was approved by the Ethics Committee of Shimane University and written informed consent was obtained from all subjects.

RESULTS AND DISCUSSION

Compared to the CT group, the T allele and TT genotype frequencies of rs1048661 were higher in patients with BRVO ($p=0.0137$ and $p=0.0203$, respectively). In subgroup analysis,

compared to the CT group, the group with BRVO with exfoliation material deposits (EX+) had significantly different allelic and genotypic frequencies ($p=0.00011$ and $p=0.000189$, respectively), while the group with BRVO without exfoliation material deposits (EX-) had no difference in allelic and genotypic frequencies ($p=0.175$ and $p=0.288$, respectively). Compared to the CT group, the frequencies of the G allele of rs3825942 and the C allele of rs2165241 were higher in the BRVO EX+ groups with borderline significance ($p=0.0933$ and $p=0.0908$, respectively), but the allelic and genotypic frequencies did not differ between any pairs of BRVO total or BRVO EX- and the CT group.

CONCLUSION

Both the BRVO EX- and CT groups, which were classified based on slit-lamp examination as not having EX, were identical except for the presence or absence of BRVO, comparison between these two groups should provide the most reliable information about the possible role of the *LOXL1* variants in BRVO. As a result, the significant difference observed in rs1048661 between the case and control groups was canceled in the analyses between the BRVO EX- and CT groups, suggesting that the percentage of the population at risk of EX is not significantly higher in the BRVO group. No association was found between BRVO and EX if LOXL1 variants were used as disease markers for clinically undetectable EX. The results suggested that LOXL1 variants, well established markers for EX, are not likely genetic markers for BRVO in Japanese subjects.