学位論文審査結果の要旨

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（学位論文審査結果の要旨）

Mutation Analysis of Thin Basement Membrane Nephropathy

【主論文審査結果の要旨】

著者らは論文において下記の内容を述べている。

Thin basement membrane nephropathy (TBMN) is characterized by the observation of microhematuria and a thin glomerular basement membrane on kidney biopsy specimens. Its main cause is heterozygous mutations of *COL4A3* or *COL4A4*, which also cause late-onset focal segmental glomerulosclerosis (FSGS) or autosomal dominant Alport syndrome (ADAS).

Thirteen TBMN cases were analyzed using Sanger sequencing, multiplex ligation-dependent probe amplification (MLPA), and exome sequencing. Ten heterozygous variants were detected in *COL4A3* or *COL4A4* in nine patients via Sanger sequencing, three of which were novel variants. The diagnostic rate of "likely pathogenic" or "pathogenic" under the American College of Medical Genetics and Genomics guidelines was 53.8% (7 out of 13 patients). There were eight single nucleotide variants, seven of which were glycine substitutions in the collagenous domain, one of which was a splice-site single nucleotide variant, and two of which were deletion variants. One patient had digenic variants in *COL4A3* and *COL4A4*. While MLPA analyses showed negative results, exome sequencing identified three heterozygous variants in causative genes of FSGS in four patients with no apparent variants on Sanger sequencing.

Since patients with heterozygous mutations of *COL4A3* or *COL4A4* showed

a wide spectrum of disease from TBMN to ADAS, careful follow-up will be necessary for these patients.

本論文は、基底膜菲薄病患者の遺伝子を解析することにより、同疾患の原因となる新規の遺伝子変異を明らかにした。また、同定された新規遺伝子変異の病原性を示唆した論文であり、学術上極めて有益であり、学位論文として価値あるものと認めた。

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