A Novel Nonsynonymous Variant of Matrix Metalloproteinase-9 Confers Risk of Idiopathic Membranous Nephritis

Yu-Huei Liu[1,2], Tze-Yi Lin[3], Cheng-Hsu Chen[4], Chang-Hai Tsai[5,6], Fuu-Jen Tsai[7,8,9,10]*

[1]Department of Medical Genetics and Medical Research, China Medical University Hospital, Taichung, Taiwan; [2] Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan; [3]Department of Pathology, China Medical University Hospital. [4]Division of Nephrology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan;[5]Department of Pediatrics, China Medical University Hospital, Taichung, Taiwan; [6]Asia University, Taichung, Taiwan; [7]School of Chinese Medicine, China Medical University, Taichung, Taiwan; [8]School of Post-Baccalaureate Chinese Medicine, China Medical University, Taichung, Taiwan; [9]Department of Biotechnology, Asia University, Taichung, Taiwan, [10]Department of Biotechnology and Bioinformatics, Asia University, Taichung, Taiwan.

Idiopathic membranous nephritis (IMN), characterized by progressive accumulation of extracellular matrix following chronic renal injuries, is one of the most common forms of autoimmune nephritic syndrome in adults. In the extracellular space, the constant turnover of liver matrix is regulated by the matrix metalloproteinase (MMP) class of enzyme. To assess whether genetic variations in MMP would result in diversity of IMN, a case-control study of 129 patients and 150 healthy individuals, was conducted. Five single-nucleotide polymorphism markers from potential fibrosis-associated genes were selected for genotyping. Among these genes, a nonsynonymous single-nucleotide polymorphism which generates the variation of 279R and 279Q in the MMP-9 gene was found to be strongly associated with the development of IMN. In contrast to major form MMP-9 (279R) that predominantly secretes out into the cell culture medium, the IMN-associated MMP-9

(279Q) variant is preferentially localized on the extracellular membranes where it exerts its proteolytic activity on pericellular substrates. In wound-healing and Boyden chamber assays, cell motility was specifically reduced with the expression of MMP-9 (279Q) as compared to the cells expressing MMP-9 (279R). These results demonstrate that the MMP-9 (279Q) variant confers a loss-of-function phenotype for MMP-9. Conclusion: We have identified a novel genetic association of MMP-9 variant with IMN. Whether the MMP-9 variant can be a new marker for IMN will be further studied.