Elucidation of the Pathogenic Mechanisms of Dementia with Lewy Bodies Based on Whole-Genome Sequence Analysis

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Dementia with Lewy bodies (DLB) is a progressive neurodegenerative disorder characterized by cognitive decline and motor dysfunction, for which disease-modifying mechanisms remain largely unclear. We previously identified two East Asian–specific rare variants associated with DLB: *MFSD3* p.C293* and *MRPL43* p.N81H. In this study, we investigated their functional roles using human neural stem cell models and genetically engineered mouse models.

CRISPR/Cas9-mediated introduction of *MFSD3* p.C293* into human neural stem cells resulted in reduced cell proliferation and impaired differentiation into neurons and astrocytes. In *Mfsd3* knockout mice, age-dependent phenotypes were observed, including ventricular enlargement, reduced hippocampal neurogenesis, and decreased locomotor activity; however, no Lewy body formation or α-synuclein accumulation was detected. *MRPL43* p.N81H mutant cells exhibited reduced mitochondrial membrane potential, whereas *MRPL43* knockout mice were embryonically lethal, indicating that *MRPL43* is essential for survival and that the p.N81H variant retains partial function.

These findings suggest that *MFSD3* and *MRPL43* variants contribute to neuronal vulnerability and mitochondrial dysfunction, respectively, but are insufficient to induce full DLB pathology in isolation. Instead, they may act as genetic susceptibility factors that require additional pathological stress, such as α-synuclein burden, to trigger disease onset. This study provides new insights into genotype-dependent vulnerability mechanisms underlying DLB pathogenesis.