Elucidation of the cell death mechanism induced by abnormal mitochondrial oligomerization of dementia-associated protein

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Frontotemporal dementia, which encompasses many cases of early-onset dementia, lacks established fundamental treatments, making the understanding of its pathogenesis an urgent priority. This study focused on mutations in mitochondrial-localized proteins associated with familial frontotemporal dementia, aiming to clarify the mechanisms that trigger neuronal cell death. Analysis using cultured cells showed that disease-associated variants display abnormal multimerization and aggregate formation, with the extent of these phenomena correlating with their ability to induce cell death. Furthermore, it was suggested that aggregate formation causes mitochondrial stress, potentially leading to cytotoxicity through interactions with specific molecules. Additionally, screening for compounds that influence mitochondrial function identified several candidates that inhibit aggregate formation and cell death. These findings suggest a new disease mechanism based on abnormal aggregates and are expected to aid in the development of FTD therapeutics.