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TDP-43 subcellular mislocalisation is correlated with loss of optineurin binding for frontotemporal dementia and amyotrophic lateral sclerosis associated *TBK1* missense variants

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State of the art: Frontotemporal dementia (FTD), a younger-onset dementia is genetically, pathologically and clinically related to amyotrophic lateral sclerosis (ALS), a rapidly progressive neurodegenerative disorder. Mutations in TANK-binding kinase 1 (*TBK1*) have been identified as a rare cause of FTD and ALS. TBK1 has known roles in inflammation and autophagy and interacts with other FTD/ALS proteins such as optineurin (OPTN): however, which of its roles are important to FTD/ALS pathogenesis remains undetermined. To date, >90 *TBK1* rare variants have been identified in FTD/ALS patients: >50% of these are missense variants of unknown significance (VUS).
Methodology: In this study, we have used a functional assay pipeline to investigate the effect of 16 *TBK1* VUS with *in-silico* evidence of pathogenicity. Our assay pipeline evaluated the effect of *TBK1* VUS on steady-state levels of TBK1, kinase activity and binding to OPTN. We also assessed a key neuropathological feature of FTD and ALS cases: cytoplasmic mislocalisation of neuronal TDP-43.
Results: We observed some *TBK1* VUS with similar effects to *TBK1* loss-of-function mutations, demonstrating decreased kinase activity and loss of OPTN binding. Known pathogenic mutations and several *TBK1* VUS increased the cytoplasmic/nuclear ratio of TDP-43 and this inversely correlated with their degree of OPTN binding but not with kinase activity.
Conclusion: These results suggest that loss of the direct interaction between TBK1 and OPTN is more critical to FTD/ALS pathogenesis than TBK1's kinase activity. Further studies are needed to elucidate how loss of TBK1 binding to OPTN leads to TDP-43 pathology and ultimately neurodegeneration.

Conflicts of interest

N/A