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Conserved gene signatures shared among MAPT mutations reveals defects in calcium signaling

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State of the art: More than 50 mutations in the *MAPT* gene result in heterogeneous forms of frontotemporal lobar dementia with tau inclusions (FTLD-Tau). However, early pathogenic events that lead to common mutations remain poorly understood. The goal of this study is to identify common molecular signatures of FTLD-Tau.
Methodology: We analyzed genes differentially expressed in induced pluripotent stem cell (iPSC)–derived cortical neurons carrying *MAPT* IVS10+16, p.P301L, and p.R406W compared with isogenic controls.
Results: We identified 275 commonly dysregulated genes across the three *MAPT* mutations. These genes were enriched among synaptic, endolysosomal, and neuronal development pathways. A subset of these genes were also found to be dysregulated in primary tauopathy (progressive supranuclear palsy) brains, suggesting we are capturing molecular signatures in a dish that are relevant to genetic and sporadic forms of tauopathy. Several of the genes were also altered in the presence of tau aggregates in a mouse model of tauopathy (Tau-P301L). Interestingly, one of these genes (*CALB1*) is the target of several FDA-approved drugs. *CALB1* plays a role in calcium dysregulation, which is altered in these mutant neurons, and many of the pathways enriched among the dysregulated genes are influenced by disruption in calcium homeostasis.
Conclusions: The results from this study demonstrate that iPSC-neurons capture molecular processes that occur in human brains and can be used to pinpoint common molecular pathways involving synaptic and endolysosomal function and neuronal development, which may be regulated by disruptions in calcium homeostasis.

Conflicts of interest

N/A