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Role of TMEM106B on neuronal susceptibility to degeneration in FTLD

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State of the art: Genome wide association studies identified numerous variants spanning the *TMEM106B* locus as a strong genetic modifier of Frontotemporal lobar degeneration (FTLD) with TDP-43 aggregates (FTLD-TDP). These variants, which are collectively referred to as a haplotype, were found to protect from disease even in carriers of progranulin (*GRN)* mutations, previously believed to be fully penetrant. Only one of the variants on the haplotype falls into the coding region of *TMEM106B* (rs3173615, c.554C>G à p.T185S), but the exact contribution and possible mechanism by which this variant contributes to disease protection in humans remains unknown.

Methodology & Results: We used a novel in-house developed CRISPR/Cas9 prime editing system to generate 3 different isogenic iPSC lines, carrying the different genotypes of the p.T185S *TMEM106B* coding variant (e.g. TT, TS and SS) and a *TMEM106B* knock out isogenic line. These iPSC lines will be differentiated into human cortical neurons to assess whether the difference in *TMEM106B* background can alter TMEM106B and/or GRN expression levels. In parallel, we will use multi-omic approaches to investigate the putative molecular changes derived from these different *TMEM106B* genotypes, which may be affecting neuronal fitness and vulnerability to disease.

Conclusion: Overall, this project will generate an invaluable series of isogenic iPSC lines carrying the only coding *TMEM106B* GWAS variant. Studying these lines will clarify the functional relevance of p.T185S in conferring protection and will allow deciphering the mechanisms by which TMEM106B modulates neuronal fitness and neuronal susceptibility to degeneration in the context of FTLD-TDP.

Conflicts of interest

N/A