Role of TMEM106B in C9ORF72-related Frontotemporal Lobar Degeneration

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Role of TMEM106B in C9ORF72-related Frontotemporal Lobar Degeneration

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Alzheimer's Society

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€ 248,451

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Research Abstract

A GGGGCC repeat expansion in C9ORF72 is the most common genetic cause of frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (referred to as C9FTD/ALS). Genetic variants of TMEM106B are associated with risk of FTLD in C9FTD/ALS patients. This grant is to establish the mechanisms by which TMEM106B variants influence this risk.

Three mechanisms by which the C9ORF72 repeat expansion might cause C9FTD/ALS have been proposed: loss-of-function by haploinsufficiency, protein toxicity by dipeptide repeat

proteins (DPRs) and RNA toxicity. Considerable evidence indicates that C9FTD/ALS may involve autophagy deficits. The presence of ubiquitinated, p62-positive DPR inclusions and TDP-43 pathology in C9FTD/ALS patients in itself is indicative of deficits in autophagy. Moreover, we have found that C9orf72 protein regulates autophagy initiation, and depletion of C9orf72 from cells to mimic haploinsufficiency induced p62 accumulations similar to the pathology found in C9FTD/ALS patients.

TMEM106B protein is localised in lysosomes and regulates lysosomal functions. Because of the role of lysosomes in autophagy we reasoned that TMEM106B might affect autophagy. We found that overexpression of TMEM106B significantly attenuated autophagy, showing that TMEM106B can regulate autophagy.
We hypothesise that (i) TMEM106B variants modify risk for C9FTD/ALS by affecting autophagy and that (ii) targeting autophagy will modify disease pathogenesis. Our aims are (1) to determine how TMEM106B is involved in autophagy, (2) to study the disease-modifying mechanisms of TMEM106B variants in cell models of C9FTD/ALS, and (3) to investigate the effect of autophagy enhancing drugs on disease pathogenesis.

Further information available at:

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