Risk and progression of frontotemporal dementia in carriers of the TMEM106B protective genotype and its relationship with TDP-43 pathology

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Recently, in the journal *Science Translational Medicine*, Marks *et al.* [2024] investigated the association of the rs3173615 polymorphism and TMEM106B aggregation in a postmortem frontotemporal dementia (FTD) lobar degeneration with TDP-43 inclusions (FTLD-TDP) brain cohort, as well as its interactions with other proteins (1). It is proposed that the accumulation of TMEM106B is a key mechanism by which its protective haplotype lowers the risk of disease and slows the progression of FTLD-TDP.

FTD is a neurodegenerative disorder characterized by progressive impairment of the frontal and temporal lobes, leading to a decline in cognitive functions. The disease commonly includes changes such as social behavior, apathy, impulsivity, language difficulties, and executive dysfunction (2). The disorder is a common form of dementia before age 65 years, comprising 10–15% of all dementia cases, after Alzheimer's disease (AD) and Lewy body dementia. FTD often affects individuals at a younger age, usually between 40 and 65 years old, although it can occur later in life (2-4). The exact cause of FTD is not fully understood, but it involves a combination of genetic and environmental risk factors (2).

Clinical subtypes comprise the behavioral variant frontotemporal dementia (bvFTD) and various forms of primary progressive aphasia (PPA): semantic dementia (SD or svPPA) and progressive non-fluent aphasia (PNFA or nfvPPA), which are part of the FTD clinical spectrum. Additionally, the logopenic variant (lvPPA) is typically associated with AD-type pathology (3,5,6).

A subset of FTD cases is characterized by atypical intracellular accumulation of the microtubule-associated protein tau (FTLD-tau), which includes specific tau isoforms resulting from the alternative splicing of exon 10 in the *MAPT* gene. The most tau-negative cases are related to transactive response DNA/RNA binding protein 43 kD (TDP-43). TDP-43 is widely expressed in neuronal nuclei and functions as a key transcriptional regulator. In FTLD-TDP, there is a loss of normal nuclear TDP-43, along with its abnormal aggregation in the cytoplasm, dendrites, axons, and nucleus. Another subtype, FTLD-FET, is associated with the FET family of RNA-binding proteins, typically located in the nucleus. FTLD-FET is usually sporadic, with subtypes classified by the morphology and distribution of neuronal cytoplasmic and nuclear inclusions. Finally, 5–10% of patients may present inclusions containing proteins from the FUS-Ewing sarcoma-TAF15 family (FTLD-FUS) (7).

FTD is estimated to be familial in approximately 20–25% of cases, often associated to autosomal dominant

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inheritance. Pathogenic variants in three genes are associated with most cases of familial FTLD: *GRN*, encoding progranulin (PGRN); *MAPT*, encoding microtubule-associated protein tau; and *C9orf72* (encoding chromosome 9 open reading frame 72), the most common genetic cause of FTLD-TDP (7).

TMEM106B is a 274 amino acid type II transmembrane protein, localized to the endosome/lysosomal compartments, expressed in neurons and glia, where TMEM106B regulates morphology, intracellular localization, movement, pH, and the expression of lysosomal proteins, such as PGRN and cathepsin D. The full-length TMEM106B presents an N-terminal cytosolic domain, a transmembrane domain and a C-terminal luminal domain with glycosylation sites, which undergoes a two-step proteolytic cleavage process to produce N-terminal and C-terminal fragments. TMEM106B is related to the brain volume [an relationship was found between TMEM106B rs1990622 and the gray matter volume of the left-sided temporal brain regions, crucial for language processing (8)]; the neuronal proportion [the variant TMEM106 rs1990621 was associated with the neuronal proportion, in high linkage disequilibrium with the TMEM106B non-synonymous variant p.T185S, which was previously identified as a protective variant for FTLD (9)]; and cognitive status [for FTD subjects, the TMEM106B rs1990622 T allele was associated with a more rapid decrease in the Mini-Mental State Examination (MMSE) score (10)]. However, the significance of the core filaments composed of TMEM106B brain tissue remains uncertain (7).

Jiang *et al.* [2022] extracted amyloid fibrils from the brains of four patients with FTLD-TDP, characterized by pathological neuronal inclusions with TDP-43. Using cryo-electron microscopy (cryo-EM), they observed that all amyloid fibrils were made up of a 135-residue carboxy-terminal fragment of TMEM106B, rather than TDP-43 (11). In fact, other studies observed that fragments derived from residues 120 to 254 in the C terminus of TMEM106B are a common feature in aging and besides several neurodegenerative disorders, such as Parkinson's disease (12-14). *Figure 1* shows the structure of TMEM106B with the N-terminal cytosolic, transmembrane, and C-terminal luminal domains. The luminal domain contains the aggregate fibril core (12,15).

Studies have demonstrated that different TMEM106B genotypes change the phenotype in individuals at risk of developing FTD in carriers of C9ORF72 expansions (16,17). These genotypes are also associated with the risk of developing a limbic-predominant TDP-43 pathology in AD, and tauopathy in some patients with a primary pathological diagnosis of FTD/amyotrophic lateral sclerosis-TDP. A more severe clinical phenotype is linked to the major risk haplotype, while the minor haplotype offers a protective effect. Moreover, a new genetic pathogenic variant of the *TMEM106B* gene (p.D252N) has been identified in patients with hypomyelinating leukodystrophy (18). Common genetic variants at the *TMEM106B* locus were first related to the risk of FTLD-TDP developing by genome-wide association studies (GWAS). The rs1990622-T allele demonstrated an odds ratio of ~1.6 for developing FTLD-TDP. Tropea *et al.* [2019] observed that *TMEM106B* variants, which increase the risk of FTLD-TDP, might also be associated with a faster cognitive decline in FTD patients, particularly within the bvFTD subgroup (10,19). Lee *et al.* [2023] determined how major genetic risk factors and ageing for dementia affect the lipidome and hippocampal proteome of healthy individuals older than 65 years. They observed that the increase in TMEM106B levels with age was specific to carriers of the single nucleotide polymorphism (SNP) rs1990622-A allele in the *TMEM106B* gene, which is linked to a higher risk of FTD, AD, Parkinson's disease, and hippocampal sclerosis as individuals age. The primary TMEM106B risk allele for dementia influenced brain lipid homeostasis, particularly impacting myelin lipid content. They concluded that TMEM106B is a key dementia risk gene affecting glial lipid metabolism (20).

In both *GRN* and *C9orf72* carriers with FTD, the *TMEM106B* gene has acted as a genetic modifier. For the *GRN* gene, a lower age at onset may be related to carrying the *TMEM106B* risk allele, and symptomatic *GRN* carriers are rarely found to be homozygous for the protective allele (21,22). Van Deerlin *et al.* [2010] showed that a single linkage disequilibrium block on chromosome 7p21, that comprises the *TMEM106B* gene, is associated with FTLD-TDP, whose variants may confer risk by increasing *TMEM106B* expression. In this study, FTLD-TDP cases were classified according to *GRN* mutations, and the association with the 7p21 locus continued in both the *GRN*-negative and -positive clusters. In addition, no significant heterogeneity was observed in the odds ratio for the SNP association between the groups. A logistic regression analysis including the SNP rs1990622 at the 7p21 locus showed no effect on the association at the *GRN* locus. However, they separately assessed mRNA expression of TMEM106B in FTLD-TDP cases with and without

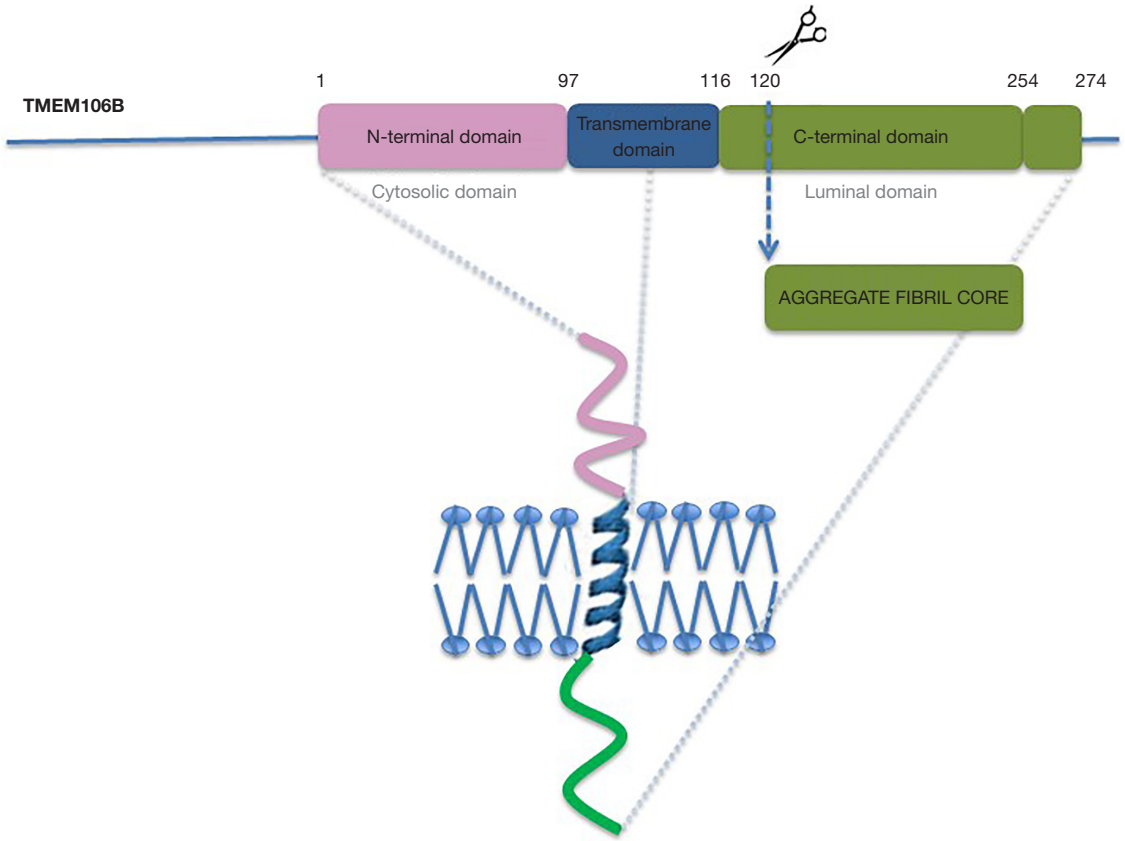

Figure 1 Schematic structure of TMEM106B. N-terminal domain, transmembrane domain, and C-terminal domain indicating the site that may become cleaved, corresponding to the aggregation-prone region.

GRN mutations. The results revealed that GRN mutants exhibited elevated TMEM106B expression compared to both FTLD-TDP cases without GRN mutations and controls. This suggests that GRN mutations may drive the increased TMEM106B expression and contribute to a higher risk for FTLD-TDP (19). In summary, the genetic relationship between TMEM106B and FTD risk determined by TDP-43 pathology is known, but the mechanism by which *TMEM106B* genetic variants influence TDP-43 fibrils remains unknown.

Marks *et al.* (1) observed that the rs3173615 minor allele (GG/SS185) was associated with longer survival after symptom onset than carriers of the major allele (CC/TT185 or CG/TS185), based on a cohort with TMEM106B rs3173615 status. Although the sample size was limited (n=228), with missing data (n=22), this result corroborates the finding that threonine at position 185 may be important to stabilize the β sheet structure of the protein during fibril formation, and carriers of the T185 allele exhibit increased lysosomal localization compared to S185 carriers (18). However, other *TMEM106B* polymorphisms are in linkage disequilibrium (LD) with rs3173615 (21); consequently, it is possible that other SNPs might also play a role in the phenotype associated with the risk allele of TMEM106B, requiring further studies.

To investigate the hypothesis that *TMEM106B* allele risk could explain protein aggregation, the authors produced an antibody against residues 191 to 206 in the TMEM106B fragment core sequence, which was able to detect all constructs but did not lack the immunogenic sequence (191 to 206 deletion). Its immunoreactivity was unaffected by the p.T185S change (23). The antibody was validated in postmortem brain tissue from the frontal cortex of two FTLD-TDP cases, which revealed TMEM106B-positive fragments of 29-kDA in the sarkosyl-insoluble fraction by western blot, and that glycosylation contributes to the higher molecular weight of the insoluble TMEM106B core fragment. However, it is important to highlight that

TMEM106B filaments were also detected in two patients with pathologically confirmed AD, suggesting no specificity with FTLD-TDP. Vicente *et al.* [2023] previously reported the use of immunoblotting to detect this TMEM106B C-terminal fragment in the sarkosyl-insoluble fraction of post-mortem human brain tissue from patients with different proteinopathies. They observed that the majority patients with GRN mutations exhibited an intense band for the TMEM106B C-terminal fragment, while control individuals either lacked this band or showed it at much lower levels. Additionally, the presence of the TMEM106B C-terminal fragment was strongly correlated with both age and the presence of the TMEM106B risk haplotype (24).

After, in a FTLD-TDP postmortem cohort, they observed that the sakosyl-insoluble 29-kDa TMEM106B core fragment deposition occurs accordingly a gene dosage-dependent manner, in which the lowest accumulation is seen in GG carriers, intermediate accumulation observed in heterozygous CG, and highest in CC carriers. In addition, the authors observed that the concentration of dimeric TMEM106B (25) was considerably lower in carriers of the risk genotype (CC) compared to the protective genotype (GG), but not the monomeric form, suggesting that dimeric TMEM106B could protect against either the formation or deposition of the core filaments, independently of the sequence of the protein. It is important to emphasize that the mechanism of TMEM106B homodimerization is not completely elucidated, but Chen-Plotkin *et al.* [2012] observed migration of the high-molecular-weight 60 kDa TMEM106B by immunoblotting, since the predicted molecular weight of the monomeric form is 31 kDa, suggesting self-association into a dimer (25).

Moreover, there was no difference in *TMEM106B* expression when evaluated at the RNA level. Nevertheless, the same pattern of sakosyl-insoluble TMEM106B core fragment deposition follows a gene dosage-dependent way in cognitively healthy individuals, suggesting that TMEM106B aggregation is not exclusive to FTLD-TDP.

The authors next examined the influence of the haplotype on the subcellular and cellular location of TMEM106B in the FTLD-TDP brain using immunohistochemistry (IHC). It is important to emphasize that IHC was previously detailed by Perneel *et al.* [2023], who investigated a huge number of commercial antibodies targeting various TMEM106B C-terminal epitopes, as well as one against the TMEM106B N-terminal domain, assessed on tissue sections from cases where the TMEM106B filament status had already been established using cryo-EM (16). Strong TMEM106B immunoreactivity was observed in numerous cell types, including large perinuclear deposits in neurons and glia, and co-localization of TMEM106B with the lysosomal hydrolase cathepsin D in microtubule-associated protein 2 (MAP2)-positive neurons, glial fibrillary acidic protein-positive astrocytes, and ionized calcium binding adaptor molecule 1-positive microglia, suggesting a position of TMEM106B in the endolysosomal transmembrane with the core domain localized to the vesicle lumen (1). In agreement with Perneel *et al.* [2023], using IHC, the intensity of immunoreactivity could not be used to differentiate risk haplotypes or disease status. However, this study showed that the presence and abundance of TMEM106B C-terminal immunoreactive aggregates correlated strongly with patient age, and all patients with FTD carriers of *GRN* mutations presented high levels of TMEM106B C-terminal, including young patients (<60 years) (26). The contribution of both the *TMEM106B* haplotype and the *GRN* rs5848 genotype to TMEM106B C-terminal abundance was evaluated in another study, revealing no association with the *GRN* risk allele but a significant association and correlation between the number of *TMEM106B* risk haplotypes and the insoluble TMEM106B C-terminal core. Individuals with two *TMEM106B* risk haplotypes had higher quantities of C-terminal compared to individuals with two protective *TMEM106B* haplotypes. It is important to highlight that comparing immunoblotting and immunohistochemistry, the authors detected higher amounts of TMEM106B C-terminal by immunohistochemistry, suggesting the existence of multiple species of TMEM106B C-terminal with possible biological implications (23).

Taking account the morphology and distribution of TDP-43 inclusions, the study revealed higher TMEM106B core deposition in FTLD-TDP type A compared to B and C, which together represent more than 95% of all FTLD-TDP cases. Type A is the more common form, related to genetic variants in *GRN* gene and a greater diversity of TDP-43 inclusion, such as neuronal intranuclear and cytoplasmatic, glial, and perivascular inclusions (26,27). This finding suggests that an elevated TMEM106B core burden could be linked to more widespread TDP-43 pathology. This hypothesis was tested by examining the relationship between the abundance of the sarkosyl-insoluble 29-kDa TMEM106B fragment and the quantity of urea-soluble pTDP-43. The analysis showed that increased TMEM106B accumulation was associated with elevated pTDP-43 levels, with results adjusted for age at death and

sex in a multivariable analysis. Nevertheless, colocalization of these two proteins was not demonstrated.

Pathological TDP-43 aggregation is linked to its loss of function, which leads to impaired nuclear clearance, aberrant splicing or incorporation of a premature stop codon in the TDP-43 target stathmin-2 (STMN2). It was demonstrated that truncated production of STMN2 transcripts is related to TDP-43 dysfunction, discerning FTLD-TDP from patients with FTLD-tau (28). The authors observed a relationship between the 29-kDa TMEM106B core and truncated STMN2 transcript, adjusting for sex, age at death, and RNA integrity number, suggesting that TMEM106B is related to TDP-43 pathology and its loss of function.

Finally, using mass spectrometry and immunoprecipitation, the authors observed that 1,309 proteins interacted specifically with TMEM106B in the sarkosyl-insoluble fraction. In a biologic pathways analysis, the enrichment interactome resulted in terms related to the FTLD-TDP pathogenic process: cytoplasmatic translation, ribosome, intracellular transport, endocytosis, and pathways of neurodegeneration. The endocytic pathway comprised dynamin proteins, epidermal growth factor receptor pathway substrate 15 (EPS15), Ras-associated binding (RAB) family members, and early endosome antigen 1 (EEA1), which are crucial for vesicle trafficking and the maturation of early endosomes. The most enriched pathway was kinesin family member 5B (K1F5B), critical for intracellular transport (29). The ribosome pathway included proteins associated with both the 40S and 60S ribosomal subunits. Within neurodegeneration-related pathways, TDP-43 interacted with insoluble TMEM106B, and many autophagy-associated proteins, such as optineurin, valosin-containing protein (VCP), TRAF family member-associated NFKB activator (TANK)-binding kinase 1 (TBK1), and huntingtin. Ultimately, proteins regulated by TDP-43 at the RNA level, such as cytoplasmic fragile X messenger ribonucleoprotein 1 interacting protein 2 (CYFIP2), were also observed. Interestingly, among the proteins immunoprecipitated with TMEM106B fragments, 43 are well-established splicing targets of TDP-43.

In conclusion, this study showed that the rs3173615 minor allele (GG/SS185) was linked to longer survival following the onset of symptoms in patients with FTLD-TDP. Additionally, the quantity of the insoluble 29-kDa TMEM106B core fragment was associated with the risk allele (CC/TT185). It also demonstrated a higher abundance of dimeric TMEM106B in GG carriers and that the aggregation of the TMEM106B filament core modulates susceptibility to TDP-43 proteinopathy. Finally, the identification of insoluble TMEM106B interactors revealed biological pathways potentially disrupted by TMEM106B deposition, providing mechanistic insight into the pathogenesis of FTLD-TDP.

The results suggest the potential of TMEM106B as a biomarker in FTLD-TDP. However, TMEM106B is localized to the late endosomal/lysosomal compartment, which makes its quantification in soluble form in biofluids difficult, such as blood and cerebrospinal fluid (CSF). In fact, a proteome study of autopsy-confirmed limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) and non-LATE-NC, using mass spectrometry, did not show adequate sensitivity to detect TMEM106B in CSF (30).

Some limitations of this study should be considered. It is necessary to investigate other polymorphisms in LD with the SNP rs3173615, and to determine how these SNPs influence TMEM106B deposition and the β sheet structure of the core during fibril formation. Furthermore, the specificity of TMEM106B pathology to FTLD-TDP should also be examined by considering other neurodegenerative diseases, and the exact subcellular localization of the TMEM106B core filaments should be identified. Even with these limitations, the findings of this study provide evidence that it is important to consider the *TMEM106B* genotype for better clinical monitoring in FTD patients with TDP-43 pathology.

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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