



# Physiological and pathological functions of *TMEM106B*: a gene associated with brain aging and multiple brain disorders

Tuancheng Feng<sup>1</sup> · Alexander Lacrampe<sup>1</sup> · Fenghua Hu<sup>1</sup>

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## Abstract

*TMEM106B*, encoding a lysosome membrane protein, has been recently associated with brain aging, hypomyelinating leukodystrophy and multiple neurodegenerative diseases, such as frontotemporal lobar degeneration (FTLD) and limbic-predominant age-related TDP-43 encephalopathy (LATE). During the past decade, considerable progress has been made towards our understanding of the cellular and physiological functions of *TMEM106B*. *TMEM106B* regulates many aspects of lysosomal function, including lysosomal pH, lysosome movement, and lysosome exocytosis. Both an increase and decrease in *TMEM106B* levels result in lysosomal abnormalities. In mouse models, *TMEM106B* deficiency leads to lysosome trafficking and myelination defects and FTLD related pathology. In humans, alterations in *TMEM106B* levels or function are intimately linked to neuronal proportions, brain aging, and brain disorders. Further elucidation of the physiological function of *TMEM106B* and changes in *TMEM106B* under pathological conditions will facilitate therapeutic development to treat brain disorders associated with *TMEM106B*.

**Keywords** FTLD · Myelination · Lysosome · *TMEM106B* · Progranulin · TDP-43 · Aging

## Introduction

### **TMEM106B is associated with brain disorders and brain aging**

Frontotemporal lobar degeneration (FTLD) is a devastating neurodegenerative disease that results in personality and behavioral changes and language disorders [50, 60]. FTLD overlaps in pathology and genetic causes with amyotrophic lateral sclerosis (ALS), and these two are often considered part of a continuous disease spectrum [45]. A large subset of FTLD patients accumulates ubiquitin-positive aggregates containing the RNA-binding protein TDP-43. In an effort to identify genetic risk factors for FTLD with TDP-43 inclusions (FTLD-TDP), *TMEM106B* was discovered as a main risk factor for FTLD with *Granulin* (*GRN*) mutations [78]. The rs1990622 single-nucleotide polymorphism (SNP), in the 3' untranslated region (UTR), is most commonly

associated with modulating the disease risk; almost all other disease associated *TMEM106B* SNPs are in linkage disequilibrium with rs1990622, making it a sentinel SNP [14, 20, 21, 42, 57, 78, 79]. While the major *TMEM106B* allele (or the most common allele, rs1990622<sup>T</sup>) acts as a risk factor, the minor allele (rs1990622<sup>C</sup>) reduces the odds of patients with *GRN* mutations developing FTLD [78]. *TMEM106B* has also been shown to affect brain size [29], neuronal proportion [43], and cognitive decline in FTLD patients [76] (Table 1). Further research has also found that *TMEM106B* might modify disease progression in ALS/FTLD patients carrying mutations in another gene, *C9ORF72* [17, 22, 77]. Despite this, surprisingly no strong link has been found between *TMEM106B* and ALS risk [32, 80], although *TMEM106B* appears to affect cognitive impairment in ALS [80] (Table 1).

In addition to ALS/FTLD, recent genome-wide association (GWAS) studies and gene expression studies have found that *TMEM106B* modulates several other neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), chronic traumatic encephalopathy (CTE), hippocampal sclerosis in aging (HS-Aging), and limbic-predominant age-related TDP-43 encephalopathy (LATE) (Table 1). In Alzheimer's disease, the major allele has been

✉ Fenghua Hu  
fh87@cornell.edu

<sup>1</sup> Department of Molecular Biology and Genetics, Weill Institute for Cell and Molecular Biology, Cornell University, 345 Weill Hall, Ithaca, NY 14853, USA

**Table 1** Association of TMEM106B with brain disorders

Disease	TMEM106B SNPs/mutations	Risk allele/ major allele	Protective allele/minor allele	Phenotypes associated with SNPs/mutations	References
FTLD- <i>GRN</i>	rs1990622	T	C	Increased risk for FTLD- <i>GRN</i> (all risk alleles)	[14, 20, 21, 29, 42, 43, 57, 76, 78, 79]
	rs1990621	C	G	Altered chromatin structure (rs1990620).	
	rs1990620	A	G	Reduced brain size (rs1990620)	
	rs1020004	A	G	Decreased neuron proportion (rs1990621)	
	rs6966915	C	T	Worse cognitive decline (rs1990622)	
	rs3173615 (T185S)	C	G	Major allele associated with later onset and age at death	[17, 22, 77]
FTLD- <i>C9ORF72</i>	rs1990622	T	C	Fewer minor allele homozygotes found in FTLD- <i>C9ORF72</i> cases	
	rs3173615	C	G	Worse cognitive decline in ALS patients (rs1990622)	[80]
ALS	rs1990622	T	C	Worse TDP-43 pathology (rs1990622)	[35, 46, 49, 64]
	rs1990620	A	G	Increased AD risk in APOE4 mutation carriers (rs1990622; rs1596014)	
	rs1595014	T	A	Reduced inflammation in LOAD (rs1990620)	
PD	rs1990622	T	C	Worse cognitive decline (rs1990622)	[76]
CTE	rs3173615	C	G	Less inflammation, ante-mortem dementia, and Tau pathology in CTE patients (rs3173615)	[5, 11]
HS-Aging	rs1990622	T	C	Increased risk and more advanced TDP-43 pathology (rs1990622)	[52, 87]
LATE	rs1990622	T	C	Increased risk (rs1990622)	[30, 51]
HLD	c.754G>A (D252N)			Hypomyelination in the brain. Delayed motor skills development	[33, 70, 84]

FTLD frontotemporal lobar degeneration, ALS amyotrophic lateral sclerosis, AD Alzheimer's disease, PD Parkinson's disease, CTE chronic traumatic encephalopathy, HS-aging hippocampal sclerosis of aging, LATE limbic-predominant age-related TDP-43 encephalopathy, HLD hypomyelinating leukodystrophy

associated with enhanced TDP-43 pathology [64]. Additionally, TMEM106B variants interact with APOE polymorphisms to confer risks in AD [35, 46]. In a recent study using an iterative weighted gene co-expression network analysis (WGCNA), a TMEM106B variant (rs1990620<sup>G</sup>) was shown to confer protection from the inflammatory subtype of Late-Onset Alzheimer's disease (LOAD) [49]. In Parkinson's disease, the *TMEM106B* major allele (rs1990622<sup>T</sup>) is associated with faster cognitive decline [76]. In chronic traumatic encephalopathy (CTE), the minor *TMEM106B* allele is associated with reduced ante-mortem dementia, reduced phosphorylated Tau pathology, reduced inflammation, and increased synaptic protein density, but has not been significantly associated with disease risk [5, 11]. The major allele of TMEM106B was also found to be a risk factor for hippocampal sclerosis in aging (HS-Aging) [52] and associated with more advanced TDP-43 pathology in old persons without FTLD [87]. Recently, researchers have discovered that many people of advanced age, especially those over 80, have TDP-43 pathology and dementia; they named this disease "limbic-predominant age-related TDP-43 encephalopathy

(LATE)" [51]. This new disease criterion contains a significant portion of patients previously considered as having hippocampal sclerosis in aging (HS-Aging) with TDP-43 pathology [51]. TMEM106B has been shown to be one of the main risk factors for TDP-43 proteinopathy in LATE [30, 51].

More intriguingly, a novel dominant SNP in TMEM106B causing an amino acid substitution D252N has been recently associated with several cases of hypomyelinating leukodystrophy (HLD) [33, 70, 84]. Unlike the previously mentioned rs1990622 sentinel SNP, D252N has a very strong disease presentation and alters the molecular function of TMEM106B, providing novel insight into the role of TMEM106B in the lysosome [19].

Additionally, a genome-wide transcriptome study associated TMEM106B with brain aging [63]. The protective variant of the TMEM106B gene was also found to confer a neuronal protection effect against general aging, independent of disease status [43]. In culmination, the last decade's worth of genetic studies has found TMEM106B to be closely linked to overall brain health, and implicated TMEM106B

as a central player in brain aging, myelination disorders, and neurodegenerative diseases.

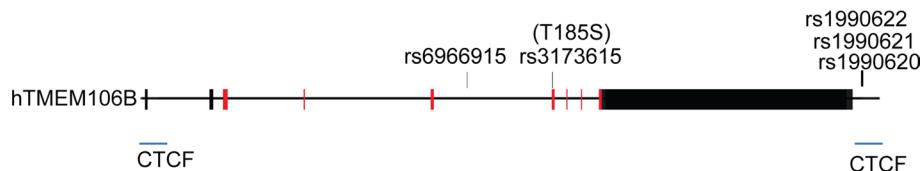
### ***TMEM106B* encodes a lysosomal membrane protein expressed by many cell types**

The human *TMEM106B* gene is comprised of nine exons located on chromosome 7p21 (Fig. 1). Alternative splicing gives rise to two *TMEM106B* mRNA isoforms, but they encode the same protein. *TMEM106B* is a type II transmembrane protein containing 274 amino acid residues, which can be divided into three domains: an N-terminal cytosolic domain, a transmembrane domain, and a C-terminal luminal domain containing five *N*-glycosylation sites [41] (Fig. 2).

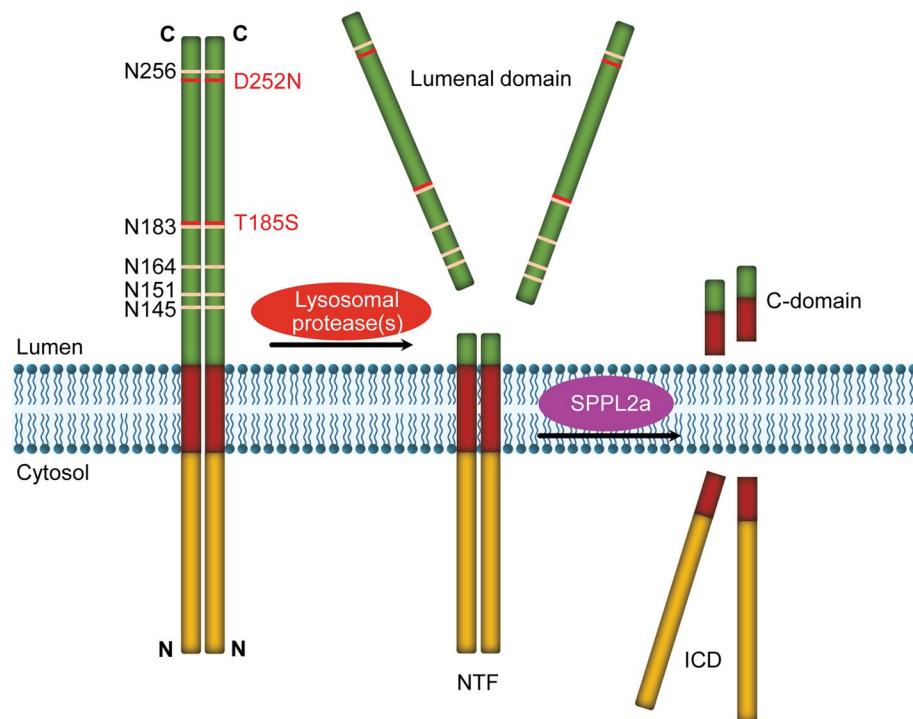
With a predicted molecular weight of 31 kDa, *TMEM106B* runs at ~43 kDa due to glycosylation [7, 10, 41]. In the central nervous system (CNS), *TMEM106B* is expressed highest in neurons and oligodendrocytes [7, 10, 19, 41]. At the subcellular level, *TMEM106B* is localized in late endosome/lysosome compartments [7, 10, 41].

### **Lysosomal function of *TMEM106B***

Lysosomes as the main degradative organelle in the cell contain many acid hydrolases that digest a variety of substrates, including proteins, lipids, glycans, and nucleic acids, which they receive from multiple pathways,



**Fig. 1** *TMEM106B* genomic structure and variants. The human *TMEM106B* gene is comprised of nine exons. The coding regions are labeled in red. The major SNPs associated with neurodegenerative diseases are indicated. The CTCF-binding sites are labeled in blue



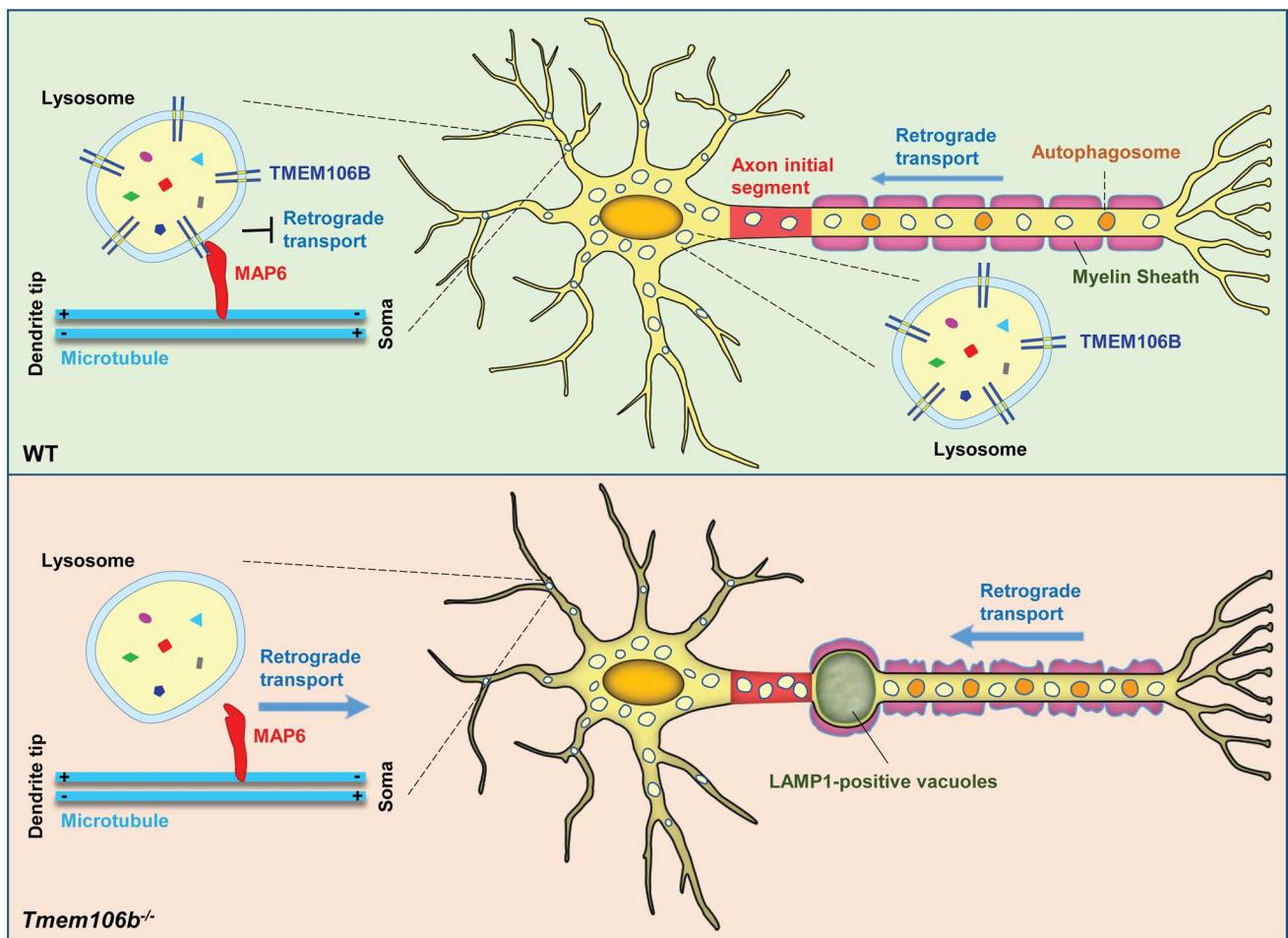
**Fig. 2** Domain structure and proteolytic processing of *TMEM106B* protein. *TMEM106B* is a type II transmembrane protein localized on the lysosome membrane, with its N-terminus facing the cytosol and C-terminus facing the lysosome lumen. The luminal domain contains five predicted *N*-glycosylation sites. Heterozygous D252N mutation in *TMEM106B* is associated with HLD. The T185S variant

has been shown to be protective towards several neurodegenerative diseases. *TMEM106B* forms homodimers and heterodimers with its homolog *TMEM106C*. *TMEM106B* is processed into an N-terminal fragment (NTF) by lysosomal proteases, which is further cleaved by SPPL2a through intramembrane proteolysis to generate intracellular cytosolic domain (ICD)

including endocytosis, phagocytosis, and autophagy [65]. In addition, lysosomes have emerged as a central signaling hub within the cell that senses and integrates multiple signals to respond to changes in the environment [65]. Lysosomes are very dynamic organelles that traffic along microtubules within the cell and constantly undergo fusion and fission [6, 59]. Lysosomal dysfunction is closely linked to neurodegeneration and mutations in the lysosome genes are frequently associated with neurodegenerative diseases [44]. During the past decade, studies by multiple groups have shown the role of TMEM106B in regulating several aspects of lysosomal function.

## TMEM106B, lysosomal morphology, and lysosome movement

Several studies in cell lines show that overexpression of TMEM106B results in lysosome enlargement [7, 10, 41], induces cell death, and enhances oxidative stress-induced cytotoxicity [21, 74]. This phenotype is also observed in primary neurons [72]. On the other hand, reduced TMEM106B expression does not appear to have an obvious effect on lysosomal size or morphology in *in vitro* studies [7, 72]. Surprisingly, loss of TMEM106B in mice leads to the formation of lysosomal vacuoles at the distal end of the axon initial segment (AIS) of motor neurons [18, 47] (Fig. 3), and in the axon initial segment in aged Purkinje cells. Since lysosome size is intricately regulated by fission events and fusion with other organelles, such as endosomes and autophagosomes



**Fig. 3** TMEM106B regulates lysosomal trafficking in neurons. In dendrites, TMEM106B interacts with MAP6 to restrict retrograde transport of lysosomes. In axons, TMEM106B regulates lysosome transport across the axon initial segment (AIS) region. TMEM106B deficiency results in increased retrograde transport of lysosomes in dendrites and reduced dendritic branching in cultured neurons. In

mouse models, loss of TMEM106B leads to the formation of LAMP1 positive lysosomal vacuoles at the AIS region in motor neurons and Purkinje neurons. This is partly due to increased retrograde transport of lysosomes along axons. TMEM106B ablation also results in alterations in the myelin sheath along axons

[16, 75], it is likely that either lysosome fusion or fission is affected by TMEM106B.

In addition to lysosome size, TMEM106B has also been shown to affect lysosome movement within the cell [18, 47]. In mammalian cells, lysosome movement is regulated by its tracking along microtubules mediated by kinesin and dynein motors [6]. The positioning of lysosomes within the cell affects many aspects of lysosomal function and cell physiology [59]. Knockdown/knockout of TMEM106B induces lysosomal clustering near the nucleus, resulting in reduced lysosomal exocytosis (fusion of the lysosome with plasma membrane) in nonpolar cells [40, 67] and in the oligodendroglial precursor cell line Oli-neu [19]. In cultured primary cortical neurons, knockdown of TMEM106B was shown to increase axonally transported lysosomes [72]. In motor neurons, TMEM106B ablation results in increased retrograde transport of lysosomes along axons, which could contribute to the formation of giant lysosomal vacuoles at the distal end of the AIS [47] (Fig. 3).

The mechanism by which TMEM106B regulates lysosome movement remains to be determined. It has been shown that TMEM106B physically interacts with microtubule-associated protein 6 (MAP6) to inhibit retrograde transport of lysosomes in neuronal dendrites [67] (Table 2, Fig. 3). In primary neurons, down-regulation of TMEM106B significantly increases retrograde transport of lysosomes in dendrites and reduced dendritic branching (Fig. 3). This phenotype can be rescued by MAP6 knockdown, or the expression of dominant-negative Rab7-interacting lysosomal protein (RILP), which has been shown to enhance anterograde lysosomal transport [67]. How TMEM106B regulates lysosome movement in axons is still a mystery. TMEM106B might have a specialized role in transporting lysosomes across AIS in motor neurons and Purkinje cells, given the unique lysosome vacuolation phenotypes in the AIS region in the TMEM106B-deficient mice [18, 47, 73].

Taken together, these studies have revealed that TMEM106B is a critical regulator of lysosome positioning

within the cell body and lysosomal transport in axons and dendrites. However, general lysosomal dysfunction has also been shown to cause the clustering of lysosomes near the nucleus [59]. It remains to be determined whether the lysosome trafficking defects in *Tmem106b*<sup>−/−</sup> cells are due to a direct regulation of lysosome movement by TMEM106B or secondary effects caused lysosomal dysfunction because of TMEM106B loss.

### TMEM106B and lysosomal pH

The lysosome is maintained at pH 4.5–5.0. Acidification of the lysosomal lumen is critical for the proper stability and activity of many lysosomal hydrolases and degradation of lysosomal substrates [75]. Lysosomal acidification is achieved by the action of vacuolar-ATPase (V-ATPase) [75]. TMEM106B was shown to interact with V-ATPase accessory protein 1 (AP1) [19, 38] and AP2M1 [72] (Table 2). Ablation of TMEM106B results in a reduction in the levels of AP1 and V0 subunits of V-ATPase, leading to impaired lysosomal acidification [38]. On the other hand, contradictory data have been reported with TMEM106B overexpression. In some studies, overexpression of TMEM106B was shown to induce cellular alkalization, and impair endosomal–lysosomal acidification [10, 41]. However, another study found that overexpression of GFP-tagged TMEM106B in murine and human lung cancer cell lines leads to increased fluorescence intensity of lysotracker compared to control cells, indicating enhanced lysosomal acidification in response to TMEM106B overexpression [40]. Similar results have been reported in HEK293T cells with the application of both pH-sensitive and pH-insensitive dyes to more accurately measure lysosomal pH [19]. Further studies are needed to resolve the discrepancies and elucidate the molecular mechanisms by which TMEM106B regulates lysosomal pH.

### TMEM106B regulates the levels and activities of lysosomal proteins

TMEM106B was shown to physically interact with the lysosomal protease cathepsin D and maintain proper cathepsin D levels in oligodendrocytes [19]. In addition to cathepsin D, other lysosomal proteins have also been shown to be affected by alteration in TMEM106B levels. In vitro, TMEM106B overexpression leads to the upregulation of lysosomal gene expression, while TMEM106B knockdown results in decreased lysosomal gene expression [40]. This is likely due to the effect of TMEM106B on the cytoplasm–nuclear translocation of the transcription factor EB (TFEB), a master transcriptional regulator for lysosomal biogenesis [40, 72]. However, conflicting results have been reported from *in vivo* studies. One study reported a decrease in the levels

**Table 2** List of TMEM106B-interacting proteins

Name	Methods	References
AP2M1	Yeast two-hybrid	[72]
CLTC	Yeast two-hybrid	[72]
VPS11	Yeast two-hybrid	[72]
VPS13D	Yeast two-hybrid	[72]
TMEM106C	Yeast two-hybrid	[72]
MAP6	Co-immunoprecipitation	[67]
CHMP2B	Co-immunoprecipitation	[36]
V-ATPase accessory protein 1 (AP1)	Co-immunoprecipitation	[19, 38]
Cathepsin D	Co-immunoprecipitation	[19]

of several lysosomal proteins, including LAMP1, and lysosomal enzymes (CatB, CatL, and DPPII) in the brain lysates of TMEM106B-deficient mice generated using the gene-trap approach [38], which still express 5–10% full-length TMEM106B protein [88]. In another study using the same gene-trap knockout line, LAMP1 levels are not altered, but the activities of lysosomal enzymes  $\beta$ -glucuronidase and  $\beta$ -hexosaminidase A are decreased in TMEM106B-deficient mice [2]. However, in two other studies using complete TMEM106B knockout mice generated using the CRISPR/Cas9 technique, increased levels of cathepsins and elevated activities of several lysosomal enzymes, including  $\beta$ -hexosaminidase A,  $\alpha$ -mannosidase, and  $\beta$ -galactosidase, have been reported [19, 47]. Thus, it is likely that the presence of residual full-length TMEM106B protein in the gene-trap line [88] is the cause for the differences in these studies. Nevertheless, in all studies, the mRNA levels of these lysosomal genes were not affected by TMEM106B ablation [18, 38, 47], indicating that TMEM106B ablation does not affect TFEB activities and instead regulates the levels of lysosomal proteins through post-transcriptional mechanisms. In addition, the protein levels of LAMP1, cathepsin D and L are all decreased in TMEM106B-deficient Oli-neu cells [19], suggesting that TMEM106B might have different effects on lysosomal proteins in different cell types.

## TMEM106B and autophagy

Autophagy is a conserved intracellular degradative process essential for cellular homeostasis and self-renewal, which is especially critical for the health of postmitotic neurons [86]. Autophagy dysfunction is tightly associated with neurodegeneration and mutations in several autophagy genes, including p62/SQSTM1, optineurin, TBK1, and ubiquilin 2 are linked to ALS/FTD [48]. In the last step of autophagy, autophagosomes fuse with lysosomes and autophagy substrates engulfed in the autophagosome membrane are degraded by lysosomal enzymes. Thus, lysosome activity is essential for the completion of autophagy flux. Although TMEM106B is not required for autophagy induction and does not localize on the autophagosome membrane, TMEM106B has been shown to regulate autophagy through modulating lysosomal functions. Loss of TMEM106B in mice significantly increases the protein levels of LC3, an autophagy marker; p62, an autophagy adaptor degraded in the lysosome; and ubiquitinated proteins in the brain lysates [18, 47]. This phenotype is further exacerbated during aging [18]. These observations support that TMEM106B influences lysosomal cargo clearance and autophagic turnover by modulating lysosomal function or autophagosome–lysosome fusion. Although, it is possible that TMEM106B might also affect other steps of autophagy.

## Regulation of TMEM106B function on the lysosomal membrane

TMEM106B has been shown to form homodimers (Fig. 2) as well as heterodimers with its homolog TMEM106C [72] (Table 2). Homodimerization of TMEM106B can be detected in western blot analysis as an SDS-resistant homodimer at ~ 75 kDa in cold conditions compared to the 43 kDa monomer when boiled [7, 10]. Thus, at the lysosomal membrane, TMEM106B is likely to function as a homodimer or heterodimer with its homologs, TMEM106A or TMEM106C, both of which have been shown to localize on the lysosomal membrane [8, 67, 72] (and our unpublished observations), although TMEM106C was shown to be in the endoplasmic reticulum (ER) compartment in one study [8].

In addition, TMEM106B is cleaved by lysosomal proteases to generate an N-terminal fragment (NTF) containing its transmembrane and intracellular domains [8]. The N-terminal fragment is further processed into a small, unstable intracellular domain (ICD) by the GxGD aspartyl proteases SPPL2a through the intramembrane proteolysis [8] (Fig. 2). Whether the TMEM106B NTF and ICD have biological functions remains to be tested. It is possible that TMEM106B processing regulates its levels on the lysosomal membrane, since too much or too little TMEM106B could have profound effects on lysosomal functions.

## TMEM106B, brain aging, and brain disorders

### Alteration of TMEM106B levels in human diseases

*TMEM106B* was first identified as a risk factor for FTLD-TDP, especially in patients with *GRN* mutations [14, 20, 78, 79]. The SNP rs1990622 in the 3'UTR region of TMEM106B was found to be the most significant [20, 78] (Fig. 1). Several studies have demonstrated that the levels of *TMEM106B* mRNA [78] and protein [10, 26] were significantly increased in FTLD patients with *GRN* mutations. A recent study has shown that the risk allele of a candidate causal variant (rs1990620) preferentially recruits the chromatin-organizing protein CCCTC-binding factor (CTCF) and forms a long-range chromatin-looping interaction within a sub-topologically associated domain (sub-TAD), which contains five CTCF-binding sites [21] (Fig. 1). One of the five CTCF sites is 48 bp away from SNP rs1990620, and the other one is located at the TMEM106B promoter [21] (Fig. 1). This indicates that TMEM106B upregulation associated with the rs1990620 risk allele is probably due to transcriptional activation. Besides chromatin structure alterations, another mechanism regulating TMEM106B levels involves microRNA-132/212 cluster, which was shown to bind to the 3'UTR of TMEM106B gene and inhibits

TMEM106B expression [10]. This microRNA is significantly decreased in FTLD-TDP patients' brains, thus leading to increased TMEM106B expression [10].

Among the associated *TMEM106B* variants, rs3173615 (encoding p.T185S) is the only coding variant. This SNP was found to be in perfect linkage disequilibrium (LD) with SNP rs1990622 [14]. Cellular studies have shown that both risk (T185) and protective (S185) TMEM106B localize in the late endosomes [7, 36]. In one study, the risk TMEM106B variant (T185) was shown to have higher expression levels than the protective allele (S185), due to a slower protein degradation rate and possible differences in glycosylation at N183 [54]. However, T185 and S185 appear to be expressed at the same levels in another study [7]. Additionally, TMEM106B has been shown to interact with CHMP2B, a component of ESCRT-III involved in multivesicular body formation and a protein mutated in FTLD, and this interaction appears to be stronger with T185 than S185 [36]. In an effort to identify gene networks associated with the risk (TT) and protective (SS) *TMEM106B* haplotypes using WGCNA, several gene clusters were found to be associated with TT or SS [61], indicating that TMEM106B SNPs could have a profound effect on gene expression in the brain.

An increase of TMEM106B protein levels was observed in several conditions with lysosomal dysfunction, such as mice deficient in the FTLD gene *GRN* or lysosomal protease cathepsin D [26]. In both cases, the upregulation of TMEM106B protein is not caused by increased transcription [26]. Instead, TMEM106B protein levels might be affected by changes in lysosomal activities. In line with this, bafilomycin treatment, which inhibits lysosomal activities by interfering with lysosome acidification, significantly increases the protein levels, but not mRNA levels, of TMEM106B [10, 41]. In addition, TFEB, a master transcriptional regulator for lysosomal biogenesis [69], does not directly regulate TMEM106B expression [40].

In summary, these studies demonstrate that TMEM106B levels can be regulated at the transcriptional level through chromatin modulation, at the mRNA level by miRNAs and at the protein level through lysosomal activities.

## TMEM106B and brain aging

Brain aging is the primary risk factor for neurodegenerative diseases. Normal brain aging and neurodegenerative disease share common pathological hallmarks, such as cognitive deficits, neuronal loss, synaptic impairment, and inflammation. A recent transcriptome-wide cerebral cortex gene expression study has shown that the TMEM106B risk variant (rs1990622<sup>T</sup>) is associated with neuronal loss, inflammation, and cognitive deficits, and selectively affects the frontal cerebral cortex of older individuals (>65 years), even without any known brain disorder [63]. The TMEM106B

rs1990622 risk allele has also been associated with worse residual cognition [82], and reduced left temporal brain size [1]. In neuropathologically normal old individuals, the TMEM106B risk haplotype (rs3173615<sup>T</sup>) is associated with reduced expression of neuronal markers and increased expression of inflammatory genes in the temporal cortex [61]. Consistent with this result, TMEM106B protective variant rs1990621, which is in high LD with the TMEM106B variant rs3173615 (p.T185S) was found to confer neuronal protection against aging [43].

In mouse models, TMEM106B deficiency leads to age-dependent ALS/FTLD pathology: including accumulation of ubiquitinated proteins, autophagy adaptor protein p62, and phosphorylated TDP-43 in the brain and spinal cord [18, 47].

## TMEM106B and TDP-43 proteinopathy

Transactive response DNA-binding protein of 43 kDa (TDP-43), a DNA- and RNA-binding protein [12, 28], has been linked to the pathophysiology of several neurodegenerative diseases such as ALS/FTLD, HS-Aging [62], and AD [13, 24]. Hyper-phosphorylation, ubiquitination, and cleavage of TDP-43 serve as a pathological hallmark for a large subset of FTLD and TDP-43 often translocates from nucleus to cytosol to form ubiquitin-positive aggregates, resulting in depletion of TDP-43 in the nucleus [53]. *TMEM106B* was first identified as a risk factor for FTLD with TDP-43 aggregates, especially in patients with *GRN* mutations [14, 20, 78, 79]. Recent genetic studies identified the TMEM106B risk allele as one of the five risk factors for neuropathological change in LATE, a disease characterized by TDP-43 proteinopathy in older adults [51]. Additionally, the TMEM106B rs1990622 risk allele is associated with severe CA1 neuronal loss in LATE-NC with hippocampal sclerosis pathology [39]. Genome-wide transcription analysis found that the *TMEM106B* risk allele enhances the expression of genes associated with myelination and lysosomal membrane proteins [85], which is associated with LATE TDP-43 burden [85].

In mouse models, TMEM106B deficiency does not affect the cytoplasmic translocation of TDP-43 or TDP-43 cleavage, but leads to the accumulation of phosphorylated TDP-43 in an age-dependent manner [18]. Since the clearance of TDP-43 relies on the autophagy-lysosome pathway [68], TMEM106B could affect TDP-43 homeostasis through regulating lysosomal functions. However, further studies are needed to determine how TMEM106B risk variants affect TDP-43 proteinopathy.

## TMEM106B and myelination

Recently, a recurrent dominant mutation, c.754G > A (p.D252N) in the luminal domain of TMEM106B was

identified in patients with hypomyelinating leukodystrophy (HLD) in several studies [33, 70, 84]. All patients with the TMEM106B D252N mutation present with congenital nystagmus and mild motor developmental delay [33, 70, 84]. Additionally, in human samples, genome-wide transcription analyses have found that the *TMEM106B* risk allele enhances the expression of genes associated with myelination [85]. These findings indicate that TMEM106B might play a critical role in myelination. This was directly tested in mouse models recently. TMEM106B deficiency in mice was reported to result in myelination defects with a significant reduction of protein levels of proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG), two membrane proteins found in the myelin sheath [19]. Moreover, TMEM106B-deficient mice show eye movement and mild motor coordination defects [19, 47]. In another study, TMEM106B deficiency was shown to alter myelination-related cellular processes including axon ensheathment and oligodendrocyte differentiation in brain transcriptomic analysis [89]. A significant loss of oligodendrocytes and a reduction in the expression levels of mature oligodendrocyte markers have been observed in the corpus callosum of *Tmem106b*–/– mice at different ages. In the same study, TMEM106B deficiency was shown to result in poor recovery from cuprizone-induced demyelination [89].

Several studies have demonstrated that lysosomes play an essential role in myelination, and lysosomal dysfunction caused by mutations in lysosomal genes leads to myelination defects [23, 27, 58, 66]. Cellular studies revealed that TMEM106B is expressed and localized to the lysosome compartment in oligodendrocytes in vivo and in vitro [19]. In the Oli-neu oligodendroglial precursor cells, TMEM106B ablation results in lysosome clustering in the perinuclear region and a decrease in lysosome exocytosis [19]. Interestingly, PLP, the main transmembrane protein found in the myelin sheath, was shown to reside in the lysosome compartment and get delivered to the myelin sheath (extension of plasma membrane) upon lysosome exocytosis [83]. This process is significantly altered by the lysosome positioning and exocytosis defects due to TMEM106B loss, leading to an increased accumulation of PLP in the lysosome compartment and decreased levels of PLP on the cell surface [19, 89] (Fig. 4). In addition, TMEM106B physically interacts with cathepsin D (Table 2) and regulates cathepsin D levels in oligodendrocytes [19]. Thus, TMEM106B affects several aspects of lysosomal function in oligodendrocytes, which is critical for proper PLP trafficking and myelination.

Recently, the effect of the D252N mutation on TMEM106B function and the lysosome has also been analyzed. It does not affect TMEM106B messenger RNA (mRNA) and protein levels in vitro [19, 34, 83]. The stability and dimerization of TMEM106B are also not affected [19], but TMEM106B processing might be slightly decreased by

D252N [19]. However, interesting phenotypes have been observed regarding lysosomal alterations induced by the D252N mutation. While the D252N mutation fails to induce lysosome enlargement when overexpressed, it results in lysosome clustering near the nucleus [19]. Furthermore, the D252N mutation abolishes lysosomal acidification induced by wild-type TMEM106B overexpression [19]. Lysosomal dysfunction and impaired lysosomal acidification have also been observed in patient-derived fibroblasts with the TMEM106B D252N mutation [34]. Based on these studies, it is likely that D252N is a loss-of-function mutation that acts in a dominant-negative manner by forming a heterodimer with the wild-type TMEM106B protein. This mutation might also affect the interaction between TMEM106B and its binding partners. However, the D252N mutation does not affect the binding between TMEM106B and vacuolar-ATPase accessory protein 1 (AP1) or cathepsin D [19].

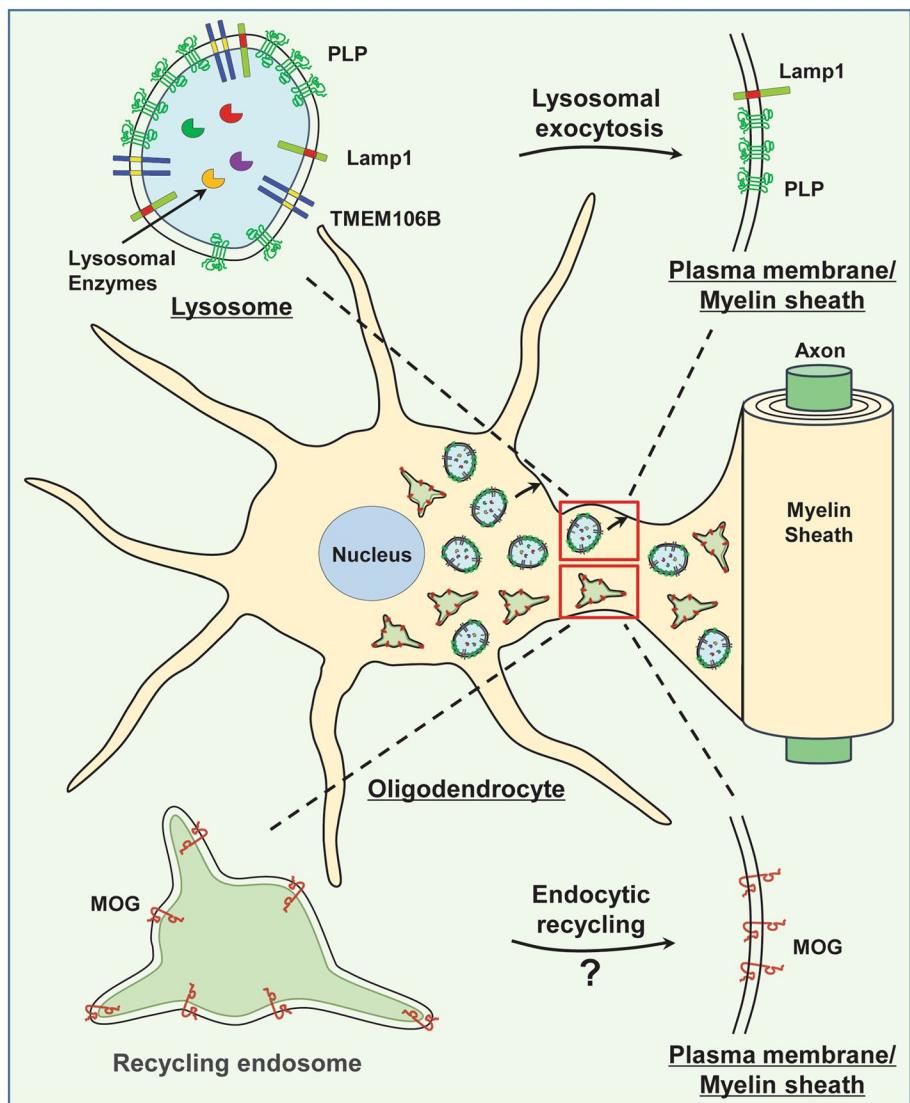
Taken together, these findings support that TMEM106B regulates myelination through modulation of lysosomal function in oligodendrocytes. Efforts to identify interactions and cellular processes affected by the D252N mutation might yield novel insights into how TMEM106B regulates lysosomal function and myelination. In addition to PLP, the levels of another myelin transmembrane protein, MOG, are also affected by TMEM106B deletion [19]. MOG, a type I transmembrane protein in the outer loop (abaxonal) region of the myelin sheath, is transported to the myelin sheath via recycling endosomes [83] (Fig. 4). It will be interesting to examine whether this process is affected by the loss of TMEM106B or the D252N mutation. Additionally, since the interaction between axons and oligodendrocytes is critical for proper myelin formation [71] and TMEM106B is highly expressed in neurons, it is possible that TMEM106B might also regulate myelination through its action in neurons.

### Genetic interaction between progranulin (PGRN) and TMEM106B

Haploinsufficiency of progranulin (PGRN) protein, caused by heterozygous mutations in the *GRN* gene, is a leading cause of familial FTLD-TDP [3, 15, 25]. PGRN, initially identified as a secreted glycoprotein, has been shown recently to play an important role in maintaining proper lysosomal function in neurons and microglia in the central nervous system (CNS), especially during aging [4, 9, 37, 56]. PGRN is comprised of 7.5 granulin repeats, which can be liberated in the lysosome compartment or extracellularly [56]. The granulin peptides have been shown to modulate the activities of several lysosomal enzymes [56].

TMEM106B was initially identified as a genetic risk factor of FTLD-TDP with *GRN* mutations [78]. The TMEM106B risk allele is associated with lower PGRN levels [14, 78]. The effect of TMEM106B on PGRN levels

**Fig. 4** TMEM106B and myelination. TMEM106B is highly expressed in oligodendrocytes and is localized in the lysosome in these cells. TMEM106B deficiency in oligodendrocytes results in lysosome clustering near the nucleus and a defect in lysosomal exocytosis, which leads to trafficking defects and decreased cell surface levels of myelin membrane protein, PLP. Additionally, TMEM106B might modulate the endocytic recycling of MOG, a type I transmembrane protein found in the myelin sheath



have been subsequently tested in cell culture and in mouse models. Cellular studies have revealed that overexpression of TMEM106B leads to an increase in PGRN levels in several cell lines [7, 10, 31] through post-transcriptional mechanisms [7, 54]. Increased levels of TMEM106B reduces the processing of PGRN into granulin peptides [31]. Although TMEM106B knockdown does not alter PGRN protein and mRNA levels in cell lines [7, 31, 41], elevated levels of full-length PGRN have been detected in the brain lysates from TMEM106B-deficient mice [47]. Increased expression of TMEM106B might also affect PGRN trafficking by impairing the endosomal–lysosomal pathway [10]. In summary, these studies support that TMEM106B affects PGRN levels and processing indirectly by altering lysosomal activities.

The TMEM106B risk allele associated with FTLD-*GRN* increases TMEM106B protein levels [10, 78]. TMEM106B protein levels are also increased in aged PGRN-deficient mice [26, 90]. Thus, modulation of TMEM106B levels might

affect disease progression of FTLD patients with *GRN* mutations. Consistent with this notion, TMEM106B transgene expression under the neuronal CamKII promoter has been shown to exacerbate lysosomal abnormalities and lipofuscin accumulation in PGRN deficient mice [90]. TMEM106B ablation in mice using the gene-trap approach, which results in the loss of 90–95% of TMEM106B protein [88], has been shown to cause changes in the lysosomal transcriptome and proteome that are opposite to those caused by PGRN deficiency [38]. From the same study, TMEM106B ablation has been shown to normalize changes in lysosomal enzyme levels and proteolysis and rescue FTLD-related behavioral deficits and retinal degeneration, but not lipofuscin accumulation in PGRN-deficient mice [38]. However, another study, using the same gene-trap line, found that TMEM106B heterozygosity fails to rescue the phenotypes of *Grn*<sup>+/−</sup> mice [2]. In addition, using independently generated mouse lines, three recent studies have shown that TMEM106B

deficiency exacerbates lysosomal abnormalities and FTLD pathology in PGRN-deficient mice [18, 81, 88]. Severe neuronal loss and glial activation have been detected in the retina, spinal cord, and brain in *Tmem106b*<sup>-/-</sup> *Grn*<sup>-/-</sup> mice. Lysosome enlargement in both microglia and astrocytes as well as increased accumulation of lysosomal vacuoles in the distal end of the axon initial segment in motor neurons have also been observed in these mice. FTLD phenotypes, such as the accumulation of ubiquitinated proteins, autophagy adaptor protein p62, and phosphorylated TDP-43, are also enhanced in the double knockout mice with a much earlier onset. Finally, severe myelination defects have also been observed in *Tmem106b*<sup>-/-</sup> *Grn*<sup>-/-</sup> mice in two of the studies [81, 88]. All of these pathological changes lead to hindlimb weakness, paralysis, and premature death in *Tmem106b*<sup>-/-</sup> *Grn*<sup>-/-</sup> mice [18, 81, 88]. The gene-trap line was used in one of the studies [88], in which a delayed onset of phenotypes was observed compared to two other lines with complete loss of full-length TMEM106B; this delay suggests that residual 5–10% TMEM106B in the gene-trap line can rescue some of the early phenotypes associated with loss of PGRN and TMEM106B [18, 81, 88]. Additionally, the gene-trap line might express an N-terminal fragment of TMEM106B fused to LacZ, which could explain some of phenotypic differences between these studies [55]. Nevertheless, results from these independently generated mouse lines strongly support that loss of TMEM106B results in lysosomal abnormalities and exacerbates phenotypes associated with PGRN deficiency. In mouse models, both up- and down-regulation of TMEM106B could have adverse effects. Therefore, TMEM106B protein levels need to be tightly regulated to ensure proper lysosomal function and brain health.

## Conclusions and perspectives

Since its association with FTLD was first identified in 2010, TMEM106B has been found to be intimately linked to brain health. We have learned a great deal about the cellular and physiological functions of TMEM106B during the past decade. A series of cellular, molecular, and genetic studies have revealed that TMEM106B plays a critical role in regulating lysosome dynamics in vitro and in vivo, and TMEM106B is associated with brain aging and multiple brain disorders. However, the exact function of TMEM106B on the lysosomal membrane remains to be determined, such as its role in lysosomal pH regulation and lysosome movement within the cell body and along axons and dendrites. The role of TMEM106B in the normal physiology of different brain cell types and neuronal subtypes still needs to be elucidated. How TMEM106B variants mechanistically alter disease-related pathology through regulating lysosomal function is still a mystery. A better understanding of

the molecular and cellular function of TMEM106B under normal and pathological conditions will help develop therapeutics for the treatment of brain disorders associated with TMEM106B.

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