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Review

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Newly identified transmembrane protein 106B amyloid fibrils in the human brain: pathogens or by-products?

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Abstract

Neurodegenerative diseases (NDs) such as Alzheimer's disease (AD) and Parkinson's disease (PD) constitute a spectrum of diseases characterized by the abnormal aggregation of specific amyloid fibrillar proteins; these include β-amyloid (Aβ) and tau in the form of the extracellular Aβ plaques and neuronal neurofibrillary tangles in AD and fibrillar α-synuclein aggregation in the form of Lewy bodies and Lewy neurites in PD. Transmembrane protein 106B (TMEM106B) is a type II transmembrane lysosomal protein that participates in lysosome morphology, localization, acidification, and trafficking; it is involved in the pathogenesis of several NDs, especially frontotemporal lobular degeneration with TAR DNA-binding protein immunoreactive inclusions (FTLD-TDP). Studies from four independent research groups revealed that the luminal domain of TMEM106B (120-254aa) forms amyloid fibrils in several brain regions in patients with a series of NDs and neurologically normal older adults. Given its potentially critical roles in the pathogenesis of NDs and brain aging, this surprising finding has focused attention on TMEM106B and suggested that it is nearly as fundamental as other pathogenic amyloid proteins (e.g., Aβ, tau, α-syn); nevertheless, new questions surrounding TMEM106B must be asked. In this review,we firstly introduce the

physiological function of TMEM106B and its involvement in NDs. Then, we elucidate the identification and cryo-electronic microscopic structure of TMEM106B fibrils and analyze the factors that contribute to the polymorphism of TMEM106B fibrils. Finally, the potential pathogenic role of TMEM106B fibrils is discussed, and the future directions for TMEM106 research in NDs are briefly summarized.

Keywords: Neurodegenerative diseases, transmembrane protein 106B, amyloid fibrils, frontotemporal lobular degeneration, lysosomal function

INTRODUCTION

Neurodegenerative diseases (NDs) are diverse and characterized by the abnormal deposition and aggregation of specific fibrillar proteins; they are thus classified by their aggregated proteins. NDs mainly consist of tauopathies, α-synucleinopathies and TAR DNA-binding protein (TDP-43) proteinopathies. The tauopathies mainly include Alzheimer's disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD), and Pick's disease (PiD). α-Synucleinopathies include Parkinson's disease (PD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB). TDP-43 proteinopathies include amyotrophic lateral sclerosis (ALS) and frontotemporal lobular dementia (FTLD)[1,2]. Patients with different proteinopathies show distinct clinical features in personality, cognition, behavior, language, and movement. Moreover, even in patients with the same proteinopathies, there is remarkable heterogeneity in clinical and pathological manifestations. For example, PD (the most common α -synucleinopathy and movement disorder) presents with bradykinesia, resting tremor, and rigidity and is pathologically characterized by the α-syn amyloid aggregation in the form of Lewy bodies (LBs) and Lewy neurites (LNs). While MSA presents as various combinations of autonomic failure, cerebellar ataxia, and parkinsonism, and its pathological hallmark is the accumulation of α-syn in oligodendrocytes as glial cytoplasmic inclusions[3]. Several lines of evidence suggest that amyloid fibrillar proteins accumulating in NDs possess prion-like seeding and propagation properties and show various biological conformations[1,4-6]; these drive the initiation and progression of NDs. In recent years, the atomic structure of the amyloid fibrils extracted from brain samples of patients with NDs was determined by cryo-electronic microscopy (cryo-EM). The results suggest that not only the amyloid fibrils composed of different proteins but also those formed by the same protein but from different NDs show distinct conformations[7-15], which further support the hypothesis of "one strain, one disease" in NDs. The elucidation of the structure of pathogenic amyloid fibrils sheds new light on the pathomechanisms and therapeutic strategies for NDs.

A genome-wide association study (GWAS) showed that variants of transmembrane protein 106B (*TMEM106B*) (located on chromosome 7p21) are risk factors for frontotemporal lobular degeneration (FTLD) with TDP-43 pathology (FTLD-TDP), especially in patients with granulin (*GRN*) mutation[16]. Many studies reported that multiple single-nucleotide polymorphisms (SNPs) of *TMEM106B* modify the disease risk for several NDs and are associated with their clinical and pathological phenotypes[17-23]. Moreover, abnormal *TMEM106B* mRNA and protein expressions were detected in NDs[16,22,24,25]. Cellular and molecular studies demonstrated that *TMEM106B* is an integral lysosomal protein and has crucial effects on lysosome morphology, localization, trafficking, and functions[26-28]. Overexpression and knockdown/knockout of *TMEM106B* resulted in lysosomal dysfunctions that are common pathological events occurring in NDs[26,27]. Thus, TMEM106B is thought to be associated with NDs because it influences lysosomal functions.

In addition to other pathogenic amyloid proteins in NDs, several research groups worldwide reported that TMEM106B forms amyloid fibril in the brains of NDs patients and neurologically normal older adults. Furthermore, the atomic structures of TMEM106B fibrils were determined using cryo-EM[29-32], which

updated our view on the involvement of TMEM106B in the pathogenesis of NDs. Therefore, this review aims to introduce the physiological function of TMEM106B and summarize the findings of research that focus on exploring the mechanism and function of TMEM106B in NDs occurrence and progression. Next, we elucidate the identification of the TMEM106B fibril and its cryo-EM structures. Finally, we outline directions for future research and raise questions needed to be addressed about TMEM106B in NDs based on the implications produced by the identification of TMEM106B amyloid fibril in the human brain.

STRUCTURE OF TMEM106B IN THE NATIVE STATE

TMEM106B is a single-pass type II membrane protein that localizes in late endosomes/lysosomes[26,27,33]. TMEM106B is expressed in many tissues and organs (https://www.ncbi.nlm.nih.gov/gene/54664), especially in neurons and oligodendrocytes in the central nervous system[26,34-36]. It consists of 274 amino acids and is divided into an N-terminal domain (NTD, 1-96 aa), a transmembrane domain (TMD, 97-117aa), and a C-terminal domain (CTD, 118-274 aa). The NTD is intrinsically disordered and locates in the cytosol[37], following the TMD across the phospholipid bilayer of late endosome/lysosome once in the form of an α-helix; the CTD in the lumen is predicted to form seven β-sheets and is prone to aggregating[31,33]. Like other membrane proteins, TMEM106B is a highly glycosylated protein with N-glycosylation occurring at Asn 145, 151, 164, 183, and 254 in the CTD[33]. Two types of glycosylation with different functions occur in TMEM106B. Noncomplex glycosylation at N145, N151, and N164 does not influence TMEM106B localization. By contrast, the deficiency of complex glycosylation at N183 disrupts the normal transportation of TMEM106B to late endosomes/lysosomes. It leads to the accumulation of TMEM106B in the endoplasmic reticulum, suggesting that N183 glycosylation is required for the anterograde trafficking of TMEM106B to late endosomes/lysosomes. The other complex glycosylation at N254 appears to directly affect the sorting of TMEM106B to endosome based on the observation that the mutant of N254 resulted in significant localization of TMEM106B to the cell surface[33,38,39].

THE PHYSIOLOGICAL FUNCTION OF TMEM106B

Little is known about the function and cellular and molecular mechanisms of TMEM106B under physiological conditions; studies suggest that TMEM106B exerts its effects on the lysosome. Overexpression of TMEM10B in neuronal cell lines resulted in decreased numbers of lysosomes in cells and increased volume of lysosomes compared to the control group[26,34]. The enlarged lysosomes were also observed in the Oli-Neu oligodendrocyte cell line when TMEM106B was overexpressed[35]. The knockdown of TMEM106B using siRNA led to an approximately 50%-70% decrease in TMEM106B expression and did not influence lysosome number and morphology[26,27]. Two possibilities may explain these unapparelled findings. One is that the residual expression of TMEM106B after it is treated with siRNA is sufficient to maintain its normal function on lysosomal number and morphology. The other is that loss of function does not influence the -TMEM106B morphology or function. However, there was a conflicting result in which the numbers of lysosomes were significantly reduced when *TMEM106B* was knocked out using CRISPR/Cas-9 in an oligodendrocyte cell line[35], suggesting potentially varying effects of TMEM106B on lysosome numbers across cell types.

In addition to influencing the morphology and numbers of lysosomes, TMEM106B modulates the positioning and trafficking of lysosome vesicles. *TMEM106B* knockdown or knockout altered the localization of lysosomes and led to the formation of clusters because of the increased number of lysosomes near the nucleus in neurons, oligodendrocytes, and fibroblasts[27,35] but did not alter cell viability[27]. Under *TMEM106B* knockdown in primary neurons, the dendritic branching (mainly distal branches) decreased, and the retrograde trafficking of lysosomes along dendrites increased, whereas the number of lysosomes taking part in anterograde trafficking was unaffected. The imbalance between anterograde and retrograde

trafficking vesicles may cause reduced branch complexity.

TMEM106B interacts with microtubule-associated protein 6 (MAP6) in the brain through its disordered NTD binding to the CTD of MAP6. Moreover, the overexpression of MAP6 in primary neurons mimicked the phenotypes of TMEM106B knockdown, and the knockdown of MAP6 rescued the dendritic arborization and the retrograde trafficking of lysosome[27]. These findings suggest that TMEM106B takes control of the dendritic lysosomal transport through its interaction with MAP6, which is critical in dendrite branching and maintenance.

Intraluminal pH is critical for maintaining normal lysosome function under physiological conditions[40,41], and TMEM106B regulates lysosome pH. Chen-Plotkin *et al.* reported that the LAMP1-positive organelles in HEK293 and Hela cells with TMEM106B overexpression were not as acidic as the control group with normal TMEM106B expression level[34], which leads to functional impairment of protein degradation. However, a study found that HEK293 cells transfected with wild-type TMEM106B presented more robust acidification than those control cells[35]. Furthermore, another study found that the deficiency of TMEM106B in primary neurons significantly impaired lysosomal acidification[28]. Vacuolar-ATPase (V-ATPase) is responsible for normal lysosomal acidification. The co-immunoprecipitation assay identified that TMEM106B interacts with accessory protein 1 (AP1, a subunit of V-ATPase) under physiological conditions. The deficiency of TMEM106B contributes to AP1 downregulation, disturbs the normal function of V-ATPase, and thus leads to lysosomal acidifying dysfunction[28]. In brief, TMEM10B plays essential roles in lysosome morphology, intracellular localization, trafficking, and acidification.

THE INVOLVEMENT OF TMEM106B IN NDS AND AGING

Although *TMEM106B* was initially identified as a risk factor for FTLD[16], studies revealed that *TMEM106B* variants are associated with varying clinical and pathological phenotypes of several NDs. Six SNPs of *TMEM106B* are thought to be associated with NDs, and five out of these are located in the non-coding regions of *TMEM106B* and do not result in the mutations of the TMEM106B protein. Nevertheless, these SNPs may regulate the expression of *TMEM106B* in NDs by influencing the alternative splicing of *TMEM106B* mRNA. Only one of the six SNPs, rs3173615, is located in the coding regions of *TMEM106B* and contributes to the nonsynonymous mutation p.T185S. The relationships between SNPs of *TMEM106B* and NDs are summarized in Table 1. *TMEM106B* is also involved in aging, one of the most potent risk factors for NDs[42].

TMEM106B in FTLD

FTLD is a group of heterogeneous and devastating neurodegenerative syndromes and is the third leading cause of dementia after AD and DLB[43]. Pathologically, it is characterized by aggressive atrophy in the frontal and temporal lobes, contributing to corresponding clinical manifestations, including progressive behavioral deficits, personality alterations, executive dysfunction, and impaired speech[44]. FTLD shows the most significant pathological variability among NDs. The predominant neuropathology in FTLD is TDP-43 immunoreactive inclusions in neurons (FTLD-TDP), accounting for about 50% of all FTLDs[45]. Moreover, FTLD-TDP is classified into five subscales (Types A to E) based on the morphology of neuronal TDP-43 immuno-positive inclusions and the affected neocortical layers[46,47]. Although most FTLD is sporadic, approximately 10%-20% of FTLD is hereditary in an autosomal dominant manner[48]. The common pathogenic genes in FTLD include *GRN*, microtubule-associated protein tau (*MAPT*), and chromosome 9 open reading frame 72 (*C9orf72*)[49-52].

Table 1. Summaries of clinical/GWAS studies about SNPs of *TMEM106B* and its relationships with NDs

NDs	TMEM106B SNPs	Cohort composition	Major allele	Minor allele	Relationships
FTLD	rs1990622	FTLD-TDP, *n* = 515; control, *n* = 2509	T	C	Major allele increases the risk of developing FTLD[16]
		FTLD, *n* = 179; control, *n* = 137	T	C	TC heterozygous carriers in FTLD show a more rapid decrease in cognitive function[20]
		FTLD-*GRN+*, *n* = 27; FTLD-*GRN-*, *n* = 23; control, *n* = 73	A	G	Individuals carrying the major allele have an earlier age at onset[53]
		FTLD, *n* = 297; control, *n* = 595	T	C	Minor allele reduces the risk of developing FTLD[55
		Discovery cohort: FTLD-*C9orf72+*, *n* = 14 Replicate cohort: FTLD-*C9orf72+*, *n* = 75	T	C	The major allele is associated with later age at onset and death in *C9orf72* expansion carriers[17]
		GRN+, *n* = 17; control, *n* = 14	T	C	In *GRN+* individuals, the major allele is associated with decreased connectivity within the ventral salience network and the left frontoparietal network[99]
		C9orf72+, *n* = 33; *GRN+*, *n* = 61; *MAPT+*, *n* = 14; control, *n* = 123	C	T	In mutation carriers, minor allele enhances the benefit of cognitive reserve and modulates the slope of the correlation between education and grey matter volume[100]
		FTLD/ALS-TDP, *n* = 90	A	G	Individuals with AA genotype have a higher risk of neuro-astroglial tauopathy[101]
	rs3173615	Cohort 1: FTLD- *C9orf72+*, *n* = 325; cohort 2: FTLD- *C9orf72+*, *n* = 586; control, *n* = 1302	G	C	Minor allele protects *C9orf72* expansion carriers from developing FTLD[59]
		Discovery cohort: *GRN+*, *n* = 382; control, *n* = 1146; replicate cohort: *GRN+*, *n* = 210; control, *n* = 1798	C	G	The minor allele is associated with lower odds of developing disease symptoms in *GRN* mutation carriers[19]
AD	rs1990622	AD, *n* = 907	T	C	Minor allele decreases the risk of developing hippocampal sclerosis[65]
		LOAD, *n* = 1133; control, *n* = 1159	T	C	In *APOE* e4 allele carriers, the minor allele has a higher frequency in AD than those without AD[63]
		Typical AD, *n* = 807; LP-AD, *n* = 151; HpScl-AD, *n* = 132; HpScl, *n* = 30	T	C	The major allele has a higher frequency in the HpScl and HpScl-AD than the typical AD and LP-AD[102]
		AD, *n* = 21982; control, *n* = 41944;	T	C	Major allele increases the risk of developing AD[21]
	rs1595014	Discovery cohort: AD, *n* = 17536; control, *n* = 36175; replicate cohort:AD, *n* = 13219; Control, *n* = 4116;	A	T	AD risk is significantly influenced by the interaction of APOE with rs1595014 in *TMEM106B*[64]
	rs1548884	Discovery cohort: AD, *n* = 154; MCI, *n* = 401; Control, *n* = 122; replicate cohort: AD, *n* = 70; MCI, *n* = 151; control, *n* = 87	C	A	Rs1548884 is associated with CSF NFL level in all individuals involved[103]
ALS	rs1990622	ALS, *n* = 85; control, *n* = 553	T	C	The major allele is associated with poor cognitive function[67]
		ALS, *n* = 110	T	C	Minor allele increases TDP-43 pathology[22]
		ALS, *n* = 865	A	G	The major allele is associated with a higher frequency of bulbar site of onset. Minor allele increases cognitive impairment[69]
PD	rs1990622	PD, *n* = 179; control, *n* = 137	T	C	PD patients carrying major alleles present a faster decline of cognitive function over time[20]
		PD, *n* = 1121; control, *n* = 829	C	T	Minor allele increases the risk for PD patients with initial symptom of rigidity/bradykinesia[104]
HS-aging	rs1990622	HS-Aging, *n* = 268; control, *n* = 2957	A	G	AA genotypes carriers have a higher risk for developing HS-Aging pathology[74]

AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; CSF: cerebrospinal fluid; FTLD: frontotemporal dementia; FTLD-TDP: frontotemporal lobar degeneration with TAR DNA-binding protein inclusions; *GRN*: granulin; GWAS: Genome-wide association study; HpScl: hippocampal sclerosis; HS-Aging: hippocampal sclerosis of aging pathology; LOAD: late-onset Alzheimer disease; LP-AD: limbic-predominant Alzheimer disease; *MAPT*: microtubule-associated protein tau; MCI: memory-predominant mild cognitive impairment; MSA: multiple system atrophy; NDs: Neurodegenerative diseases; NCI: neuronal cytoplasmic inclusions; NFL: neurofilament light chain; SNPs: Single-nucleotide polymorphisms; TMEM106B: transmembrane protein 106B; PD: Parkinson disease; TDP-43: TAR DNA-binding protein 43.

A GWAS identified susceptibility loci for FTLD-TDP and found that three SNPs (rs1990622, rs6966915, and

rs1020004) in *TMEM106B* correlated with increased risk of FTLD-TDP. The expression level of *TMEM106B* mRNA in the frontal cortex was significantly higher in FTLD-TDP patients, particularly those with GRN mutations, than in healthy controls (HCs)[16], suggesting that genetic variants in TMEM106B are risk factors for FTLD-TDP. Another study reported that the expression of TMEM106B protein in the brains of FTLD-TDP patients with *GRN* mutations was also higher than that of HCs and other NDs[24]. *GRN* mutation carriers with homozygotes for the major (risk) allele of rs1990622 showed earlier age at onset and increased disease penetrance than heterozygotes and homozygotes for the minor (protective) allele of rs1990622[53,54]. While another study found no relationship between rs1990622 SNP in TMEM106B and age at the onset of FTLD[55]. The genetic polymorphisms of *TMEME106B* are associated with lower serum *GRN* mRNA levels in *GRN* mutation carriers. There was a negative correlation between *TMEME106B* mRNA and *GRN* mRNA levels in the peripheral blood of patients with FTLD[53,54], suggesting that TMEM106B may exert its effects on the phenotypes of FTLD by *GRN* expression. A neuroimaging study demonstrated that the gray matter volume of several brain regions affected in FTLD (including the frontal and temporal lobes) was significantly smaller in FTLD patients with AA (risk allele of rs1990622 in *TMEM106B*) than in FTLD patients with AG/GG[18]. The major allele of rs1990621 (another SNP of *TMEM106B*) correlated with more rapid cognition decline in FTLD patients[20]. However, rs1990621 was identified as a protective variant for FTLD and was associated with increased neuronal proportion in another study[56].

The hexanucleotide repeat GGGGCC in the *C9orf72* gene is the most common genetic cause of familial FTLD and ALS[57,58]. Unlike the conditions in FTLD mentioned above, the major allele of rs1990622 in *TMEM106B* associates with later age of onset and death of FTLD patients with *C9orf72* mutation and a later age at death, while *TMEM106B* rs1990622 SNP shows no influence on age at onset or death of FTLD-TDP patients without *GRN* or *C9orf72* mutation[17]. The genotype of *TMEM106B* in FTLD-TDP patients appears to protect patients with *C9orf72* mutation, suggesting the complexity of TMEM106B regulation in FTLD. In addition, the frequency of the minor allele homozygote of rs3173615 (contributes to the nonsynonymous mutation p.T185S) is obviously reduced in patients with *C9orf72* mutation in comparison with HCs, which suggests that those expressing homozygote of the minor allele are less likely to develop FTLD[59,60]. An *in vitro* study found that Hela cells transfected with the T185 vector showed higher expression of TMEM106B than cells transfected with the S185 vector because the degradation rate of S185-TMEM106B was faster than T185-TMEM106B[61]; these findings suggest a mechanism mediating different risks of FTLD resulting from *TMEM106B* rs3173615 variants.

TMEM106B in other NDs

Several lines of evidence also suggest a role for TMEM106B in other NDs. Three SNPs of *TMEM106B* are associated with AD, the most common ND and the leading cause of dementia worldwide[62]. These include rs1595014, rs1990620, and rs1990622 [Table 1]. Although genotype and allele frequencies of rs1990622 do not differ between AD patients and HCs when the status with or without the APOE4 allele is not considered, the frequencies of the major allele homozygote of rs1990622 were significantly higher in AD patients carrying APOE4 allele than HCs. These findings suggest *TMEM106B* genetic variants might modify AD by interacting with APOE4[63]. A similar study revealed that rs1595014 in *TMEM106B* is a risk modifier for AD through its mutual effect with APOE4[64]. Another study found that AD patients with the rs1990622 major allele haplotype were more likely to develop TDP-43 pathology than those carrying the minor allele[65], suggesting that the *TMEME106B* variant influences the pathological phenotype of AD. A bioinformatics analysis demonstrated that the signal pathways associated with immune function and neuroinflammation are upregulated in late-onset AD patients harboring the risk haplotype of rs1990620 in *TMEM106B*[66]. The TMEM106B expression level was lower in several brain regions and cell types in AD patients than in HCs[25], supporting the implication of TMEM106B in AD pathogenesis.

ALS is a fatal ND affecting motor neurons in the brain and spinal cord; its clinical and pathological features overlap with FTLD-TDP[57]. Similar to the phenomenon observed in FTLD, the major allele of rs1990622 on *TMEM106B* promotes cognitive decline as measured by the Mini-Mental State Examination and the Montreal Cognitive Assessment in ALS[20,67] and PD[20,68]. However, another study found that patients with ALS harboring the major allele of rs1990622 showed better cognition but worse motor functions than patients homozygous for the minor allele[69]. Among ALS patients, minor allele homozygous carriers developed more severe TDP-43 pathology than major allele homozygotes or major and minor allele heterozygotes with or without adjustment for the *C9orf72* mutation[22]. *TMEM106B* knockdown phenocopied this result *in vitro*[22], suggesting that variants of *TMEM106B* affect TDP-43 pathology in ALS by regulating TMEM106B expression levels.

Chronic traumatic encephalopathy (CTE) is an ND most often identified in postmortem autopsies of individuals exposed to repetitive head impacts. The clinical features of CTE are often progressive, leading to dramatic changes in mood, behavior, and cognition, often resulting in debilitating dementia[70]. The characteristic neuropathological findings of CTE include phosphorated-tau accumulations involving superficial cortical layers commonly located at the depths of the cerebral sulci and in perivascular spaces[71]. Among pathologically-identified CTE patients, there were significantly fewer homozygous carriers of the minor allele of rs3173615 in *TMEM106B* than those without CTE pathology. Moreover, the tau pathology appears to be most severe in homozygous carriers of the major allele, while the pathology was mildest in the homozygous carriers of the minor allele[72]. This finding suggests that *TMEM106B* variants modify tau pathology in CTE patients. However, another study reported that the genetic variations of rs3173615 in *TMEM106B* in CTE patients were not distinct from neuropathological negative controls[73]. Nevertheless, among neuropathologically verified CTE patients, the dorsolateral frontal cortex in the minor allele carriers presented slighter phosphorylated tau pathology and neuroinflammation, and higher synaptic protein density than the major allele carriers[73]. In addition, rs1990622 in *TMEM106B* (the top SNP risk factor identified for FTLD-TDP[16]) increases the risk of developing hippocampal sclerosis of aging (HS-aging)[74,75] and limbic-predominant age-related TDP-43 encephalopathy (LATE)[76,77].

Together, variants of *TMEME106B* are genetic modifiers of risk for NDs, including AD, ALS, PD, CTE, HS-aging, and LATE. Furthermore, the genotype variations of *TMEM106B* influence several clinical and pathological phenotypes of these NDs.

TMEM106B in brain aging

Aging is the most critical risk factor for most of NDs[42]. Aging brains without known disorders share characteristics with NDs, including mitochondrial dysfunction, protein homeostasis imbalance, and disturbed intercellular communication[78]. Protein aggregation, thought to be a pathological hallmark for NDs, also occurs in the brains of clinically normal older adults; these aggregates include Aβ plaques, neurofibrillary tangles composed of tau, LBs, and LNs composed of aggregated α-syn, and TDP-43 immunoreactive inclusions[79-81].

Like NDs, the genotype polymorphism and its function were explored in normal aging populations. A study leveraging RNA sequencing data revealed that the temporal cortex of normal older adults with different haplotypes of rs3173615 in *TMEM106B* had distinct gene expression patterns[82]. Another study found that *TMEM106B* and *GRN* variants synergistically influenced the aging brain's transcriptome[83]. Consistent with the results in FTLD, reduced left hemisphere volume was observed in the general population with *TMEM106B* rs1990622 risk allele[84]. These data suggest the involvement of the *TMEM106B* genetic variation in brain aging.

IDENTIFICATION AND CRYO-EM STRUCTURE OF TMEM106B FIBRILS

Abnormal cerebral aggregations of pathogenic proteins (Aβ, tau, α-syn, and TDP-43) in NDs were found in the form of amyloid fibrils resistant to sarkosyl[85-88]. Thus, the inclusions composed of pathogenic fibrillar proteins are considered the pathological hallmark of NDs. With the rapid development of equipment and technology of cryo-EM, the atomic structures of brain-extracted Aβ fibrils was elucidated in most NDs[14], tau fibrils in all tauopathies[7-9,11,12,89], α-syn fibrils in common α-synucleinopathies[10,15], and TDP-43 fibrils in ALS were determined[13]. The cryo-EM structure determination of these pathogenic proteins strengthens our understanding of the molecular pathogenesis of NDs and contributes to developing antibodies and small molecules targeting filamentous aggregation to inhibit further aggregates formation or facilitate aggregates degradation. A previously unknown amyloid fibril, formed by the luminal domain of TMEM106B, in the brain of several ND patients and normal older adults was identified by several independent groups[29-32]. Information about all the donors with TMEM106B fibrils from the four groups is summarized in Table 2. Donors with NDs included: AD, including sporadic AD and sporadic early-onset AD; tauopathies, including AGD, aging-related tau astrogliopathy, and CBD; familial frontotemporal dementia and parkinsonism linked to chromosome 17 caused by *MAPT* mutations (FTDP-17), limbic-predominant neuronal inclusion body 4R tauopathy (LNT)[12], primary age-related tauopathy (PART), and PSP; α-synucleinopathies, including sporadic or familial PD, PDD, DLB, and MSA; TDP-43 proteinopathies, including ALS, FTLD-TDP with different subtypes of TDP-43 pathology; pathological aging (PA), and vascular dementia (VaD).

EXTRACTION AND IDENTIFICATION OF TMEM106B FIBRILS

The extraction protocols for TMEM106B fibrils from the four groups were similar, as were the other amyloid fibrils (i.e., Aβ, tau, ad α-syn). Nevertheless, there are some differences, including the time when sarkosyl was added, the concentration of sarkosyl and its incubation time with homogenates, centrifugation speed and time, and the treatment of pronase. The methods used to identify the previously unknown TMEM106B fibrils differed among the studies. Cryo-EM and mass spectrometry were used to identify the protein that forms the previously unsolved amyloid fibrils in Fan *et al.* and Chang *et al.*[31,32]. The other two groups adopted model building and specific peptide searching[29,30].

CRYO-EM STRUCTURE OF TMEM106B POLYMORPHS

Six polymorphs with three folds (called folds I, II_a, II_b, and III) of TMEM106B fibrils were found in human brains [Figure 1A and B, Table 2]. Four polymorphs consist of single protofilament (S-I, S-II_a, S-II_b, and S-III), and the remaining two polymorphs comprise double protofilaments of fold I (D-I_a and D-I_b). The fibril core of all polymorphs is composed of residues 120-254 of TMEM106B, forming 17-19 β-strands and folds into a five-layer structure. The three folds' structure is divided into the N-terminal region (S120-T166), the middle region (A167-M210), and the C-terminal region (Y211-G254), which form the first two layers, the fifth layer, and the central two layers of the well-ordered fibril core, respectively. There are two subtypes of fold II (II_a, II_b) because of the difference in A167-I187.

All polymorphs share two structural characteristics. One is the glycosylation at N145, N151, N164, and N183; the other is the disulfide bond formed between C214 and C253. Four singlets share the same N-terminal region and present distinct structures in the middle region and slight structural differences in the C-terminal region [Figure 1C]. Both doublets comprise two protofilaments of fold I but with different interfaces [Figure 1B]. The interface of D-I_a consists of two positively-charged amino acids (K178 and R180) of the two protofilaments and an unknown additional density (possibly an anion), whereas that of D-I_b composes of a hydrophobic interaction between M207 and Y209.

Table 2. Summaries of information for donors withTMEM106B fibrils

Case	Disease	Age (yr)	Gender	TMEM106B Polymorphs	FH	T185S SNP	Brain region	Reference
1	AD	79	M	S-I, D-I_a	No	SS	Frontal cortex	Schweighauser *et al.*[29]
2	FAD	67	F	S-I, D-I_a	Yes	TT	Frontal cortex	Schweighauser *et al.*[29]
3	EOAD	58	F	S-I, D-I_a	No	TT	Frontal cortex	Schweighauser *et al.*[29]
4	PA	59	M	S-I, D-I_a	No	TS	Frontal cortex	Schweighauser *et al.*[29]
5	CBD	74	F	S-I, D-I_a	No	TS	Frontal cortex	Schweighauser *et al.*[29]
6	CBD	79	F	S-I, D-I_a	No	TS	Frontal cortex	Schweighauser *et al.*[29]
7	FTDP-17T	55	M	S-I, D-I_a	Yes	TT	Temporal cortex	Schweighauser *et al.*[29]
8	AGD	85	M	S-III	No	TS	Nucleus accumbens	Schweighauser *et al.*[29]
9	AGD	90	M	S-I, D-I_a	No	TT	Nucleus accumbens	Schweighauser *et al.*[29]
10	LNT	66	F	S-I, D-I_a	No	TT	Frontal cortex	Schweighauser *et al.*[29]
11	ARTAG	85	F	S-III	No	SS	Hippocampus	Schweighauser *et al.*[29]
12	PD	87	M	S-III	No	SS	Cingulate gyrus	Schweighauser *et al.*[29]
13	PDD	64	M	S-I, D-I_a	No	TT	Amygdala	Schweighauser *et al.*[29]
14	FPD	67	NA	S-III	Yes	SS	NA	Schweighauser *et al.*[29]
15	DLB	74	M	S-III	No	SS	Frontal cortex	Schweighauser *et al.*[29]
16	DLB	73	M	S-I, D-I_a	No	TS	Frontal cortex	Schweighauser *et al.*[29]
17	MSA	85	F	S-III	No	SS	Putamen	Schweighauser *et al.*[29]
18	MSA	70	M	S-I, D-I_a	No	TS	Putamen	Schweighauser *et al.*[29]
19	MSA	68	F	S-II_a, S-II_b	No	TT	Putamen	Schweighauser *et al.*[29]
20	FTLD-TDP-A	66	F	S-I, D-I_a	Yes	TS	Frontal cortex	Schweighauser *et al.*[29]
21	FTLD-TDP-C	65	F	S-III	No	SS	Frontal cortex	Schweighauser *et al.*[29]
22	ALS-TDP-B	63	F	S-III	No	SS	Motor cortex	Schweighauser *et al.*[29]
23	Normal control	75	M	S-I, D-I_a	NA	TS	Frontal cortex	Schweighauser *et al.*[29]
24	Normal control	84	M	S-I, D-I_a	NA	TS	Frontal cortex	Schweighauser *et al.*[29]
25	Normal control	101	M	S-I, D-I_a	NA	TT	Frontal cortex	Schweighauser *et al.*[29]
26	FTLD-TDP-A	60	M	S-I, D-I_a	Yes	TT	Frontal cortex	Chang *et al.*[31]
27	FTLD-TDP-A	55	F	S-I, D-I_a	Unknown	TS	Frontal cortex	Chang *et al.*[31]
28	FTLD-TDP-A	60	F	D-I_a	Yes	TT	Frontal cortex	Chang *et al.*[31]
29	FTLD-TDP-A	89	M	S-I, D-I_a	No	TS	Frontal cortex	Chang *et al.*[31]
30	FTLD-TDP-A	48	F	D-I_a	Yes	TT	Frontal cortex	Chang *et al.*[31]
31	FTLD-TDP-B	62	M	?	No	TS	Frontal cortex	Chang *et al.*[31]
32	FTLD-TDP-B	74	F	S-III	No	SS	Frontal cortex	Chang *et al.*[31]
33	FTLD-TDP-C	69	M	S-I, D-I_a	No	TT	Frontal cortex	Chang *et al.*[31]
34	PSP	68	M	S-I	NA	NA	Caudate	Chang *et al.*[31]
35	PSP	75	M	S-I, D-I_a	No	TS	Frontal cortex	Chang *et al.*[31]
36	DLB	68	M	S-I, D-I_a	No	NA	Frontal cortex	Chang *et al.*[31]
37	FTLD-TDP-A	86	M	S-I, D-I_a, D-I_b	No	TT	Medial frontal gyrus	Jiang *et al.*[30]
38	FTLD-TDP-B	76	F	S-I, D-I_a, D-I_b	No	TS	Medial frontal gyrus	Jiang *et al.*[30]
39	FTLD-TDP-C	65	M	S-I, D-I_a, D-I_b	No	TS	Medial frontal gyrus	Jiang *et al.*[30]
40	FTLD-TDP-D	64	F	S-I, D-I_a, D-I_b	Yes	TS	Medial frontal gyrus	Jiang *et al.*[30]
41	PDD	70	F	S-I, D-I_a	No	NA	Frontal cortex	Fan *et al.*[32]
42	Normal control	71	M	S-I	NA	NA	Temporal cortex	Fan *et al.*[32]
43	Normal control	101	M	S-III	NA	NA	Temporal cortex	Fan *et al.*[32]

AD: Alzheimer's disease; AGD: argyrophilic grain disease; ALS: amyotrophic lateral sclerosis; ARTAG: aging-related tau astrogliopathy; CBD: corticobasal degeneration; DLB: dementia with Lewy bodies; EOAD: sporadic early-onset Alzheimer's disease; FAD: familial Alzheimer's disease; FH: familial history; FPD: familial Parkinson's disease; FTDP-17T: familial frontotemporal dementia and parkinsonism linked to chromosome 17 caused by *MAPT* mutations; FTLD-TDP-A: familial frontotemporal lobar degeneration with TDP-43 inclusions type A; FTLD-TDP-B: familial frontotemporal lobar degeneration with TDP-43 inclusions type B; FTLD-TDP-C: sporadic frontotemporal lobar degeneration with TDP-43 inclusions type C; FTLD-TDP-D: familial frontotemporal lobar degeneration with TDP-43 inclusions type D; LNT: limbic-predominant neuronal

inclusion body 4R tauopathy; MSA: multiple system atrophy; NA: not appliable; PA: pathological aging; PART: primary age-related tauopathy; PD: sporadic Parkinson's disease; PDD: sporadic Parkinson's disease dementia; PM: polymorphs; PSP: progressive supranuclear palsy; SNP: single nucleotide polymorphism; VaD: vascular dementia. TMEM106B fibrils are indicated according to whether they comprise one (S) or two (D) protofilaments and their protofilament fold (I-III).

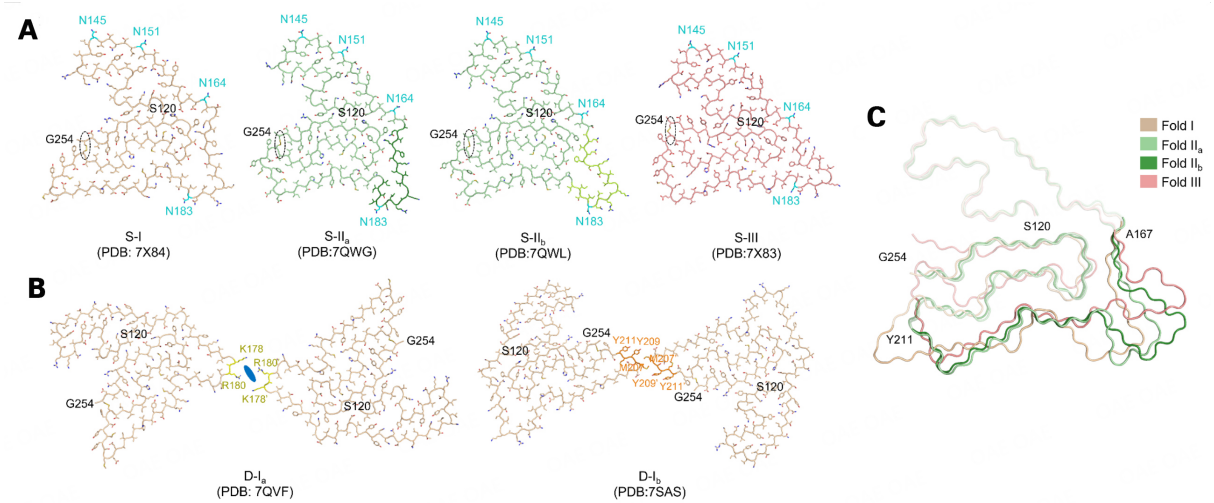

Figure 1. Polymorphs of *ex vivo* TMEM106B fibrils. A: Singlet of *ex vivo* TMEM106B polymorphs. The residues with glycosylation, N145, N151, N164, and N183, are highlighted in cyan. The dashed oval indicates the disulfide bond between C214 and C253; B: Doublet of *ex vivo* TMEM106B polymorphs. The residues comprising the interface of D-Ia and D-Ib are highlighted in yellow and orange, respectively. The blue oral indicates the unknown density comprising the D-Ia interface; C: Overlay of Folds I, IIa, IIb, and III. The N-terminal region (S120-T166), the middle region (A167-M210), and the C-terminal region (Y211-G254) of the three folds are indicated by different transparency. Side chains in (A) and (B) are shown as sticks.

The TMEM106B fibril formation process is unknown. An *in vitro* study found that TMEM106B could be cleaved into the luminal domain and an N-terminal fragment by unknown lysosomal proteases at uncertain amino sites and is further cleaved by SPPL2a, resulting in the generation of the intracellular cytosolic domain[90]. In the native state, CTD of TMEM106B is predicted to form seven β-sheets and is prone to aggregate[91]. In the fibrillar state, TMEM106B consists mainly of the CTD (120-254aa) but with β-sheets rearranged. The N-terminal Ser120 is deeply buried inside the TMEM106B fibril core, precluding additional undetermined residues. Therefore, the identification of TMEM106B fibrils suggests two implications. One is that only CTD is enriched in TMEM106B aggregates, and the other is that before forming amyloid aggregates, the luminal domain is cleaved off at Arg119.

POLYMORPHISM COMPARISONS BETWEEN TMEM106B FIBRILS AND OTHER AMYLOID FIBRILS

Cryo-EM and solid-state nuclear magnetic resonance studies revealed that different proteins or the same protein could form amyloid fibrils with several structural polymorphs in different diseases or under different *in vitro* conditions [Figure 2]. For example, *ex vivo* tau fibrils from various tauopathies show distinct folds and represent different polymorphs, on which basis the classification of tauopathies based on the biological conformation of tau fibrils was established[7-9,11,12,89]. Similarly, α-syn forms many fibril polymorphs in different α-synucleinopathies and under different *in vitro* conditions[10,15,92-94]. In contrast, although TMEM106B can form polymorphic fibrils, different TMEM106B polymorphs share a similar curling stone-like fold. The limited folding of TMEM106B may be related to its extensive glycosylation at Asn residues, the preformed disulfide bond, and other potential PTMs. Moreover, no relationship between the fold of TMEM106B and NDs was observed. For example, fold I could be found in AD, CBD, PDD, DLB,

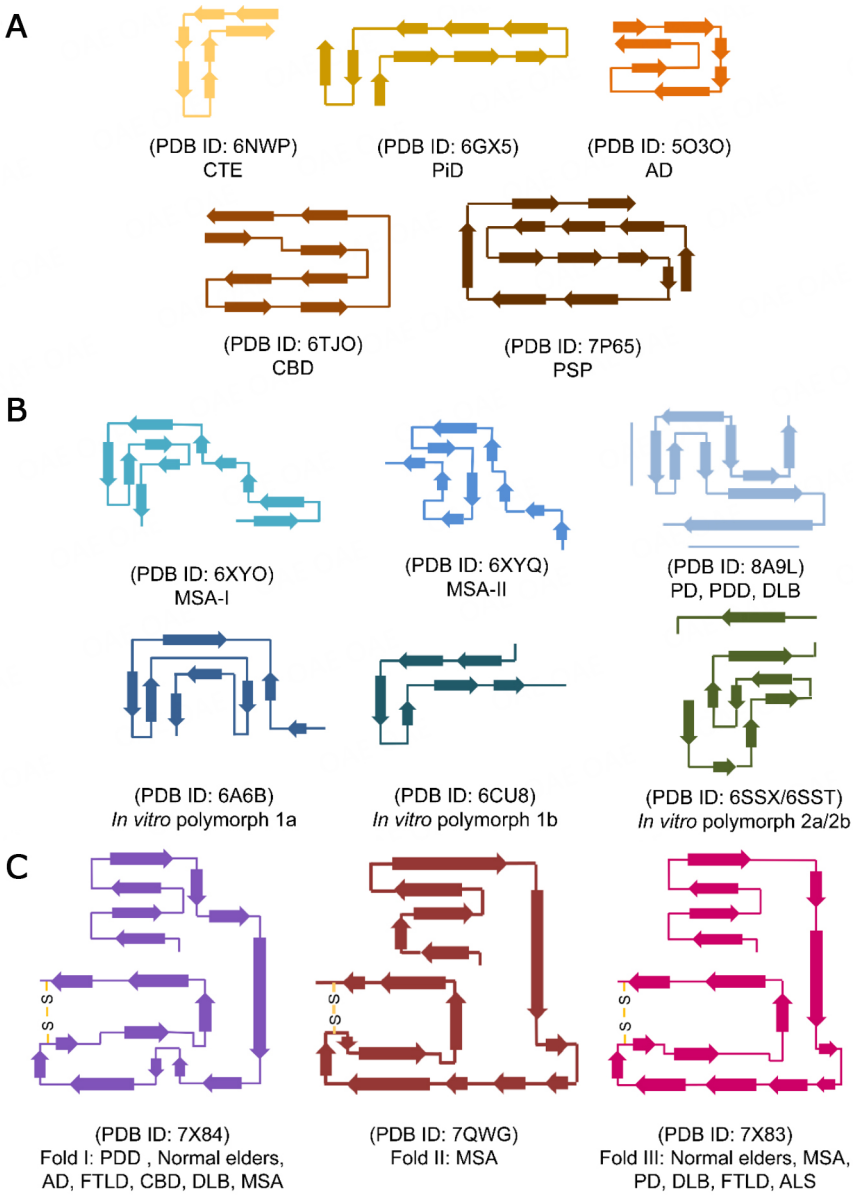

Figure 2. Comparison of the structural polymorphism of amyloid fibrils formed by tau, α-syn, and TMEM106B. The topology diagrams show different polymorphic structures of brain-extracted tau fibrils (A), brain-extracted and *in vitro* assembled α-syn fibrils (B), and brain-extracted TMEM106B fibrils (C). AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; CBD: corticobasal degeneration; CTE: chronic traumatic encephalopathy; DLB: dementia with Lewy bodies; FTLD: frontotemporal lobar degeneration; MSA: multiple system atrophy; PD: Parkinson's disease; PDD: Parkinson's disease with dementia; PiD: Pick's disease; PSP: progressive supranuclear palsy.

MSA, PSP, PA, AGD, LNT, FTDP-17T, FTLD-TDP, and normal older adults. The same ND could possess different TMEM106B folds; for example, all three folds were observed in MSA.

TMEM106B POLYMORPHISM IS ASSOCIATED WITH *TMEM106B* VARIATION

The minor allele of rs3173615 contributing to the nonsynonymous mutation p.T185S in TMEM106B was identified as a protective factor for FTLD[60,61]. The genetic phenotypes of p.T185S were recorded in 38 of 43 donors with TMEM106B fibrils. The TT homozygotes, TS heterozygotes, and SS homozygotes accounted

for 34%, 42%, and 24% percent, respectively [Figure 3A]. Interestingly, similar to the genetic variation of *TMEM106B*, the distribution of TMEM106B fibril folds differs, with fold I being the most common, followed by folds III and II [Figure 3B]. Moreover, though independent from conditions of NDs, the folds of TMEM106B fibrils are associated with TMEM106B p.T185S variation. Specifically, fold I predominantly exists in individuals with TT and TS, while fold III predominates in subjects with SS [Figure 3C]. Thus, TMEM106B p.T185S variation is critical in forming different TMEM106B fibril folds. There is clinicopathological heterogeneity across patients with NDs carrying different alleles of TMEM106B p.T185S and the degradation variation of T185-TMEM106B protein and S185-TMEM106B protein[60,61]; future research should address whether the formation of the three folds differs and whether the three folds exert different influences on ND pathogenesis and the aging process.

IMPLICATIONS AND FUTURE DIRECTIONS

Unsurprisingly, TMEM106B aggregates into amyloid fibrils in several NDs and normal older subjects because its genetic variation is associated with several clinicopathological phenotypes of NDs and normal older brains. However, different, even contradictory, conclusions about the TMEM106B fibrils were made by different groups. Because TMEM106B fibrils were found in older individuals with or without NDs but not in younger subjects, Schweighauser *et al.* concluded that TMEM106B fibrils are age-dependent and unrelated to diseases[29]. In contrast, Jiang *et al.* insisted on the pathological role of TMEM106B fibrils in FTLD-TDP because they found TMEM106B fibrils only in patients with FTLD-TDP and not in normal older adults and patients with VaD or PART[30]. To investigate the implication of TMEM106B fibrils, Fan *et al.* summarized information from donors from four studies and found that the age of donors with NDs was significantly younger than that of normal older adults, suggesting a correlation of TMEM106B fibril formation with NDs[32]. Nevertheless, based on the scant data about TMEM106B fibrils in the pathogenesis of NDs, the links between TMEM106B aggregates and other pathogenic proteins of NDs remain unknown.

Because the genotype of *TMEM106B* is related to clinicopathologies of NDs and contributes to the polymorphism of *ex vivo* TMEM106B fibrils, it is unlikely that TMEM106B fibrils are simply by-products of aging. Though TMEM106B fibrils also form in normal older adults, we could not exclude its potential pathogenic effects because aging itself is a primary risk factor for NDs[42]; pathogenic fibrillar proteins such as α-syn, tau, and TDP-43 are also present in aged individuals without NDs[79,80,95,96]. Indeed, the finding of TMEM106B fibrils would evoke enthusiasm in functional studies of TMEM106B in aging and diseased conditions.

The function of TMEM106B fibrils could be explored from the following aspects in the future. First, it is essential to determine whether TMEM106B fibrils influence the positron emission tomography imaging for amyloid aggregates such as Aβ and tau in NDs. Second, given that TMEM106B fibrils are present in the brains of NDs and normal older adults, it is vital to determine whether TMEM106B fibrils are pathological aggregates or simply by-products of normal aging. Therefore, future studies need to determine whether TMEM106B fibrils are neurotoxic and cause neurodegeneration, as other pathological amyloid fibrils do. Third, because TMEM106B amyloid fibrils were recently identified in the human brain, the distribution pattern of TMEM106B aggregates in the brain of normal older adults and NDs should be established, as Braak staging of α-syn pathology in PD and tau pathology in AD did[97,98]. In addition, it is essential to determine whether TMEM106B aggregates are co-pathologies of other pathological amyloid aggregates in the brain of NDs. Finally, it is critical to measure TMEM106B levels in biological samples such as cerebral spinal fluid and serum from patients with NDs and age- and sex-matched HCs; doing so will determine whether TMEM106B could be a potential biomarker for ND diagnosis.

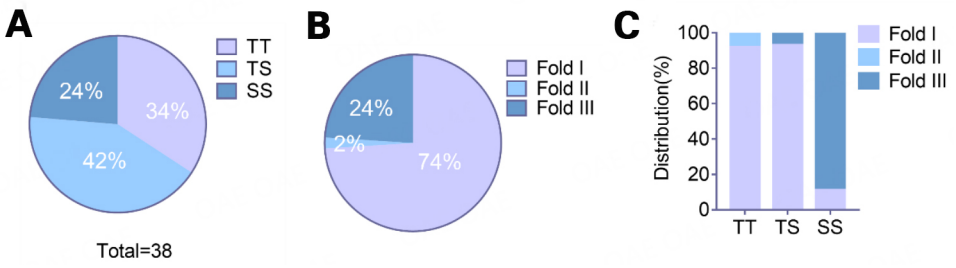

Figure 3. The distribution of TMEM106B p.T185S variation and TMEM106B fibril fold. A: TMEM106B p.T185S variation distribution in 38 donors with TMEM106B fibrils. B: TMEM106B fibril folds distribution in patients with NDs and normal older adults. C: TMEM106B fibril folds distribution in donors with different TMEM106B p.T185S variations.

In addition to functional exploration, several other questions about TMEM106B fibrils need to be investigated. First, *in vitro* replications of the TMEM106B fibril experiments must be performed to elucidate the molecular mechanisms and conditions for the fibril formation. Second, the relationship or interaction between TMEM106B aggregation and other pathogenic proteins of NDs needs to be studied. Finally, current antibodies were designed for native TMEM106B protein, and there is an urgent need for antibodies specifically targeting TMEM106B inclusions.

CONCLUSION

TMEM106B is a type II membrane protein that participates crucially in lysosome morphology, intracellular localization, trafficking, and acidification. It forms amyloid fibrils in the brains of patients with many NDs and neurologically normal older adults. Because genotype variation of TMEM106B is associated with the clinicopathological phenotypes of multiple NDs and contributes to the polymorphism of TMEM106B fibrils, it is plausible to speculate that TMEM106B fibrils are possible pathogens rather than just by-products produced during the development and progression of NDs and aging. It is also possible that the polymorphisms of TMEM106B fibrils resulting from the genetic variation of TMEM106B play critical roles in the clinicopathological heterogeneity of NDs. The investigations of the functions and roles of TMEM106B fibrils in NDs and aging are urgently needed.

DECLARATIONS

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Author's contributions

Wrote the manuscript: Fan Y, Zhao W

All authors contributed to the manuscript discussion and editing: Fan Y, Zhao W, Ni Y, Liu Y, Tang Y, Sun Y, Liu F, Yu W, Wu J, Wang J

Supervised the manuscript writing: Wang J

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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