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Heterogeneity of Parkinsonism in Familial Frontotemporal Dementia: Insights from Genetic Clues on the Pathogenesis

Chin-Hsien Lin*

Department of Neurology, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

Abstract

Frontotemporal dementia (FTD) is a clinically, genetically and pathologically heterogeneous disorder characterized by personality changes, language impairment, and deficits of executive functions, often overlapped with Parkinsonism syndrome and motor neuron disorder. Owing to the advancement in the field of molecular genetics in the familiar forms of FTD, several recent breakthroughs have provided notable insights into the pathogenesis of this neurodegenerative disorder. Nevertheless, Parkinsonism in FTD has received relatively less attention. Given that Parkinsonism feature is found in approximately 15-20% of patients with FTD, there is a need to understand Parkinsonism in FTD in order to obtain a better landscape of this disease spectrum. Recent advances have revealed mechanistic links between Parkinsonism and frontotemporal dementia, as well as between other neurodegenerative diseases, such as amyotrophic lateral sclerosis. Here, we summarize recent genetic advances and molecular findings in familial FTD with Parkinsonism and delineate the mechanisms underlying this overlapped neurodegenerative disorder.

Keywords: Frontotemporal dementia; Parkinsonism; Gene; Pathogenesis

Introduction

Neurodegenerative disorders are a major health problem with a prevalence of 135 million people affected worldwide, that is estimated to double by 2050, based on World Health Organization predictions [1]. Specific protein inclusions and depositions causing neuronal dysfunction define most neurodegenerative diseases at the pathological level, and the clinical picture is generally defined by the affected brain regions. In the past 30 years, the genetic causes of inherited forms of neurodegenerative disorders have been identified and the molecular components of the inclusions have been discovered. In most cases, pathogenic mutations cause disease through an overproduction of the amyloidogenic protein or an increase in the protein's propensity to aggregate, with resulting neurodegeneration. A major class of neurodegenerative diseases, collectively known as tauopathies, is characterized by intracellular inclusions consisting of an abnormally modified microtubule-binding tau protein. Primary tauopathies are a major class of frontotemporal lobar degeneration (FTLD) neuropathology and can present clinically with several forms of frontotemporal dementia [2] and parkinsonian syndromes (i.e., Progressive Supranuclear Palsy Syndrome, PSP; Corticobasal Syndrome, CBS) [3]. Uncovering these neurodegenerative disease-causing genes and understanding the molecular functions of encoded proteins will shed light on the mechanisms that underlie the sporadic forms of disease.

Frontotemporal dementia denotes a clinical disorder involving neurodegeneration of the frontal and temporal cortices, leading to behavioral changes and language disturbances in the presence of relatively intact memory and visuospatial functions. FTD accounts for 5-15% of all cases of dementia and is the second most common cause of dementia in the age group of less than 65 [4]. FTD is clinically divided into a behavioral variant FTD (bvFTD) and primary progressive aphasia [5]; the latter can be further subdivided into semantic dementia [6], progressive non-fluent aphasia and logopenic progressive aphasia [5]. Compared with the most common Alzheimer's dementia, FTD has an increased association with parkinsonism and, in some cases, with motor neuron disease, especially amyotrophic lateral sclerosis (ALS) [7]. Parkinsonism is usually present in patients with bv FTD, but is rarely seen in those with primary progressive aphasia [8]. Parkinsonism features may present before, during, or after the development of behavioral or language disturbances in patients with FTD. The extrapyramidal system symptoms present as bradykinesia, rigidity, and abnormal posture but rarely as tremor. This overlapped clinical spectrum of FTD with Parkinsonism, ranging from typical Parkinson's disease to parkinsonism-plus syndromes, such as PSP and CBS, has increased the clinical variability of this neurodegenerative disorder (Figure 1) [9,10].

The heterogeneity of FTD is also reflected in post-mortem pathology findings. The subtypes of underlying pathological changes in patients with FTD are classified based on the pattern and constituents of major protein depositions in neurons and referred to as FTLDs [11]. The main category is FTLD with tau pathology (FTLD-tau), in which neurons and glial cells contain inclusions of hyperphosphorylated tau protein [12]. More than half of FTLD patients present with tau-negative but ubiquitin-positive inclusions, referred to as FTLD-ubiquitin (FTLD-U). In 80–95% of this group, inclusions consist of transactive response DNA-binding protein 43 kDa (TDP-43) [7], referred to as FTLD-TDP [13]. The remaining TDP-43–negative FTLD-U cases have inclusions of fused-in-sarcoma protein (FUS), referred to as FTLD-FUS (Figure 2) [14]. However, the inclusion protein of a small number of FTLD-U patients remains unclear. Of note, the pathology findings for most patients with the logopenic progressive aphasia variant are Alzheimer's disease pathology with β-amyloid accumulations [15]. One recent study even reported α-synuclein neuronal inclusions in patients with FTD [16].

***Corresponding author:** Chin-Hsien Lin, Department of Neurology, National Taiwan University Hospital, Taipei 100, Taiwan, Tel: +886-2-23123456; Fax: +886-2-23418395; E-mail: chlin@ntu.edu.tw

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Parkinsonism is found in approximately 15-20% of patients with FTD [6,17], but few studies have focused on the clinical and genetic aspects of parkinsonism in FTD. The clinical, genetic, and pathological overlap between FTD and parkinsonism syndrome often leads to extensive phenotypic variability, even among different members of the same family who carry an identical disease mutation. For this reason, we aim to highlight recent genetic advances in familial FTD with parkinsonism and delineate the mechanisms underlying the extreme phenotypic heterogeneity that characterizes this disease.

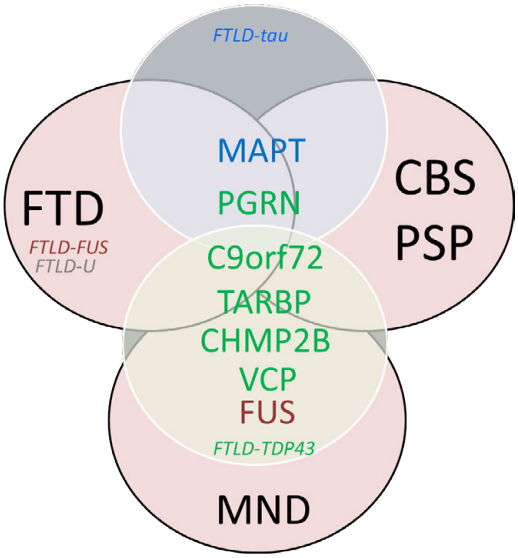

Figure 1: Clinical, genetic and pathological spectrum of frontotemporal lobar degeneration with Parkinsonism syndrome and motor neuron disorder.

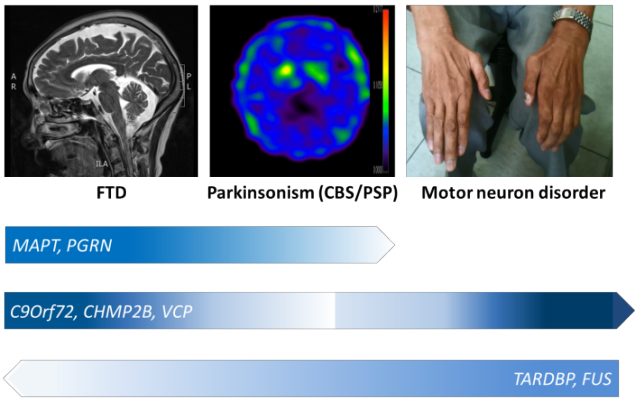

Figure 2: Main clinical features in monogenic forms of frontotemporal dementia with overlapped syndromes.

Genetics of FTD with parkinsonism

About 40% of FTD patients have at least one relative with dementia, and in 10-15%, family history is consistent with an autosomal dominant inheritance [18]. These families are characterized as having at least three affected family members in two generations specifically with FTD, motor neuron disease, or one of the parkinsonism syndromes, i.e., PSP or CBS. Among the different subtypes of FTD, bv FTD is the most prominent with family history (~ 30-50%) and combined with features of parkinsonism, while semantic dementia appears to be the least hereditary subtype of FTD (<20%) [19]. Currently, the best understood forms of autosomal dominant FTD associated with parkinsonism are those linked to chromosome 17, with mutations in the microtubule-associated protein tau (*MAPT*) and progranulin (*PGRN*) genes, and to chromosome 9, with mutations in the chromosome 9 open reading frame 72 (*C9ORF72*) gene [20]. Since 1998, when the *MAPT* gene was first linked to familial FTD with parkinsonism [21], several other genes have been identified, including chromatin-modifying protein 2B (*CHMP2B*), valosin-containing protein (*VCP*), transactive DNA-binding protein (*TARDBP*), and *FUS* (Table 1) [7,20,22-24].

MAPT

More than 50 mutations in the *MAPT* gene have been identified in families with FTD and parkinsonism linked to chromosome 17q (FTDP-17), with accumulation of hyperphosphorylated tau protein in neurons and/or glial cells [25]. The frequency of *MAPT* gene mutations is highly variable, ranging from 0-3% in sporadic FTD to 9-21% in familial cases (Table 1). The mode of inheritance is autosomal dominant. For FTDP-17 patients with parkinsonism as the initial presentation, most missense mutations are in exon 10 of the *MAPT* gene [10,26,27]. The penetrance of *MAPT* mutation carriers is more than 95% and the clinical presentation is variable and can include an initially good response to levodopa therapy, mimicking Parkinson's disease [27]. The age of onset varies by specific mutation and within the same family carrying the same mutation, but in general, disease onset is between ages 45 and 60 (Table 1). The parkinsonism features of *MAPT* mutation carriers include relatively symmetric bradykinesia, axial and limb rigidity, and postural instability but rarely resting tremor. Although patients may initially show some responses to levodopa, it is not sustained [28]. There is no phenotype–genotype correlation in *MAPT* mutation carriers; however, it has been previously shown that the dementia-dominant group correlates with the H1/H2 genotype of *MAPT* gene while the parkinsonism-dominant group correlates with the H1/H1 genotype [29].

Genes	Inheritance	Mutation frequency	Penetrance	Onset age	Associated symptoms
MAPT	AD	9-21% in familial FTD, 0-3% in sporadic FTD	>95%	45-60 Y/O	bvFTD, PPA, PSP, CBS, seizures, AD
PGRN	AD	4-23% in familial FTD, 2-8% in sporadic FTD	50% at 60 Y/O, 90% at 70 Y/O	35-83 Y/O	bvFTD, AD, PD, PSP, CBS
C9Orf72	AD	18-30% in FTD-MND, 12-18% in familial FTD, 2-4% in sporadic FTD	Incomplete	33-75 Y/O	Often combined with MND (or ALS)
CHMP2B	AD	Rare in FTD	N.A.	N.A.	Often combined with MND (or ALS)
VCP	AD	Extremely rare in isolated FTD >50% in IBMPFD	100% for IBMPFD, 30% for FTD	40-55Y/O	
TARDBP	AD	2-3% in familial FTD-MND, rare in isolated FTD	N.A.	N.A.	Often combined with MND (or ALS)
FUS	AD	<3% in familial FTD-MND	N.A.	N.A.	Often combined with MND (or ALS)

Table 1: Summary of genes associated with Parkinsonism with frontotemporal dementia.

Alternative splicing of exons 2, 3 and 10 of the *MAPT* gene gives rise to six isoforms of tau protein: three isoforms containing three amino acid repeats [16] and three isoforms with four repeats (4R). Tauopathies are classified by the predominance of tau isoforms found in cytoplasmic inclusions: those with inclusions predominantly composed of tau with 3R tau, those with predominantly 4R tau, or those with an equal ratio of 3R:4R tau [30]. The axonal protein tau is involved in the establishment and maintenance of neuronal morphogenesis through the activity of binding microtubules, which are regulated by the levels and sites of phosphorylation [31]. Tauopathies are believed to be caused by aberrant hyperphosphorylation of tau, leading to the assembly of variable neurotoxic tau aggregates and deposition of insoluble tau fibers in both neurons and glia (Figure 3) [32]. *MAPT* pathogenic mutations are thought to cause disease by either 1) inhibiting the normal microtubule-binding function of tau, 2) promoting tau protein aggregation, or 3) affecting the splicing of exon 10 to result in imbalances between 3R/4R tau isoforms [33]. As a result, specific neuropathological findings (e.g., tau isoform predominance, inclusion morphology/ultrastructure) vary for each specific mutation but universally include neuronal and glial tau inclusions together with neurodegeneration throughout the CNS, with a particular propensity for frontal and temporal neocortex, limbic structures, and basal ganglia [34].

Among parkinsonism syndromes caused by *MAPT* mutations, PSP and CBS are 4R tauopathies, which commonly combine the cognitive and behavioral features of FTD. PSP is pathologically characterized by intra-neuronal globose tau inclusions in the brainstem, subthalamic nucleus, and dentate nucleus of the cerebellum and non-neuronal inclusions, i.e., glial "tufted astrocytes" and oligodendrocytic "coiled bodies" in the white matter of the neocortex [35]. The most common clinical presentation of PSP is an atypical Parkinsonian syndrome characterized by prominent axial rigidity, early falling, oculomotor palsy and poor response to dopaminergic therapy. Overlapping syndromes of PSP and FTD, especially bvFTD, are largely due to *MAPT* mutations, especially p.delN296, p.S305S and p.N279K mutations [26,27]. However, no clear association has been identified among the presence, onset, and severity of cognitive decline in PSP patients with *MAPT* mutations [10]. In addition to familial cases, polymorphisms in the *MAPT* gene have been linked to increased risk for sporadic PSP. A recent genome-wide association study found a link between increased risk for sporadic PSP and a haplotype of an inverted sequence of polymorphisms in linkage disequilibrium, i.e., the H1 haplotype, and several variants in *MAPT* [36]. These findings support the role of *MAPT* in both familial and sporadic cases of PSP overlapped with FTD.

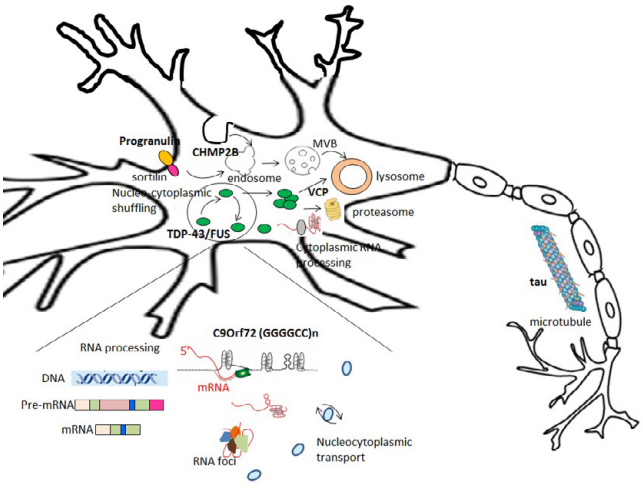

Figure 3: Overview of events in the pathogenesis of frontotemporal dementia with overlapped syndromes. Interference with normal endosomal or autophagic lysosomal protein degradation is caused by mutations in valosin-containing protein (*VCP*), charged multivesicular body protein 2b (*CHMP2B*) and, potentially, TAR DNA-binding protein 43 (TDP43) and FUS. Abnormal RNA processing, which yields erroneously assembled proteins and toxic RNA species, is caused by mutations in chromosome 9 open reading frames 72 (*C9ORF72*) and potentially *TARDBP*, which encodes TDP43 and FUS. A sortilin-mediated endocytosis of prgranulin (*PRGN*) determines the intra-cellular level of progranulin protein, which is vital for the neuronal survival. Through both gain- and loss-of-function mechanisms, these primary pathogenic changes result in progressive cellular failure that is characterized by protein clumping, aggregate formation, and endoplasmic reticulum stress. Disruption of microtubules, the main axonal architecture and transporting system, caused by mutations in microtubules-associated protein tau (*MAPT*), results in denervation of neurons (such as the cortical and lower motor neuron) or muscle.

CBS, another 4R tauopathy presenting as a parkinsonism syndrome, has a considerable clinicopathological overlap with PSP. CBS is associated with a large burden of tau-positive diffuse "astrocytic plaques" and "ballooned neurons" in the grey matter of limbic and neocortical structures and with tau-positive "coiled bodies" and astrocytic tau inclusions in white matter [35]. The basal ganglia and brainstem contain hyperphosphorylated tau inclusions as well, and sometimes the morphology is difficult to distinguish from PSP [35]. One recent study evaluating parkinsonism in patients with FTD showed that 22% (70/319) of patients demonstrated parkinsonism features [17]. Specifically, among 70 FTD patients with parkinsonism, 15 were clinically diagnosed as CBS and 7 initially diagnosed as PSP. A recent study also has shown that CBS could be an initial presentation of mutations in exon 10 of the *MAPT* gene [37]. These findings highlight the phenotypic heterogeneity and clinical overlap of syndromes caused by *MAPT* mutations.

PGRN

Since the discovery in 2006 of *PGRN* mutations in FTD patients with ubiquitin-positive, tau-negative inclusions, [38,39] more than 70 pathological mutations have been reported. The mode of inheritance is autosomal dominant. Progranulin protein is a secreted growth factor with unclear function that is highly expressed in neurons of the cerebral cortex and hippocampus and in the cerebellum [40]. The post-mortem findings of patients with *PGRN* mutations are ubiquitin-positive inclusions that do not contain progranulin [38]. These pathology observations are consistent with the fact that most *PGRN* mutations are nonsense, frameshift, or splice-site mutations producing mutant mRNAs, which are degraded by nonsense-mediated decay that prevents expression of truncated proteins [38,39]. Therefore, neurodegeneration results from a partial loss of progranulin function rather than from abnormal toxic gain of function and aggregation of the mutant protein.

Mutations in the *PGRN* account for up to approximately 4-23% of familial and 2-8% of sporadic patients with FTD (Table 1). *PGRN* mutations show an age-dependent penetrance, with 50% at age 60 and 90% at age 70 [2]. The clinical presentation in patients with *PGRN* mutations is highly variable. Age at symptom onset varies significantly, ranging from 35 to 83 years, with an average of 60 years. The most common clinical presentation in patients carrying *PGRN* mutations is bv FTD, followed by progressive non-fluent aphasia and CBS [2,41]. In a study recruiting 24 families including 32 symptomatic *PGRN* mutation carriers, parkinsonism features were reported in about 40% of patients, and 3.3% were clinically diagnosed as CBS [2]. In addition, 25% of patients with *PGRN* mutations have hallucinations and delusions as

the predominant symptoms, leading to a misdiagnosis of dementia with Lewy bodies [42]. Furthermore, an Alzheimer's dementia-like phenotype with episodic memory deficit, which occurs in 10-30% of patients with FTD, has also been reported as an initial clinical feature of the c.154delA mutation of *PGRN* [43].

Because the penetrance is not 100% and all reported mutations cause a progranulin haploinsufficiency, other factors may influence progranulin expression in patients carrying *PGRN* mutations. Genetic variants in *TMEM106B*, [44] a gene encoding the still uncharacterized transmembrane protein 106B, are reported to delay the onset of disease in *PGRN* mutation carriers by increasing levels of progranulin [45,46]. The expression level of progranulin is also regulated by factors that mediate progranulin endocytosis, including microRNAs (e.g. miR-29b and miR-107) and sortilin, a receptor for neurotrophic factors (Figure 3) [47-50]. However, no obvious modulatory effects have been observed of the *MAPT* haplotype or ApoE genotype on the clinical presentation of *PGRN* mutation carriers [51,52]. Recently, a complete progranulin deficiency due to a homozygous *PGRN* mutation was found to cause the rare lysosomal storage disease neuronal ceroid lipofuscinosis, suggesting that lysosomal storage disorders and *PGRN*-associated FTD may share a common mechanism [53].

C9ORF72

In 2011, two independent groups identified a heterozygous expanded hexanucleotide repeat (GGGGCC, G4C2), located between the non-coding exons 1a and 1b of the *C9orf72* gene on chromosome 9, as a cause of familial FTD with or without ALS [7,20]. The inheritance pattern is autosomal dominant, although the penetrance is not complete (Table 1). The number of repeat units of the *C9orf72* expansion in healthy controls is 2-24, but the repeat numbers can range from several hundred to thousands of copies [7,20]. So far, there is no clear evidence for genetic anticipation, although some studies have identified earlier disease onset in subsequent generations [54].

C9orf72 repeat expansions are about as common as mutations in the *MAPT* gene and *PGRN* gene in patients with familial FTD (Table 1). The clinical phenotype is highly heterogeneous and variable even within families affected by the same mutation. The most common clinical presentations are bv FTD, followed by motor neuron disorder, especially ALS (Figure 2) [55]. The mean age at onset is around 55 years (33-75 years). Previous reports have shown that *C9orf72* repeat expansions contribute to 18-30% of cases of familial FTD with motor neuron disorders and to 12-18% of those involving familial FTD (Table 1). Parkinsonism is reported in about 30-48% of patients with *C9ORF72* expansions [56,57]. Most patients present with levodopa-unresponsive akinetic–rigidity features, and tremors are usually not associated [58-60]. During the course of the disease, most patients eventually develop some abnormalities of behavior, language, and cognitive changes. Compared to *MAPT* and *PGRN* mutation carriers, cases involving *C9Orf72* mutations rarely present as CBS or PSP syndromes [61].

The function of the C9orf72 protein is still largely unknown, and the pathogenesis underlying the *C9orf72* mutation remains unclear. Both haplo-insufficiency through loss of gene expression [62,63] and gain-of-function mechanisms with secondary RNA toxicity caused by sequestration of RNA-binding proteins have been reported [64]. The pathological hallmarks of patients carrying abnormal GGGGCC expansions of *C9orf72* are TDP-43 immunoreactive inclusions, which have been observed in many cerebral structures, including the cerebral cortex, hippocampus, basal ganglia, substantia nigra and lower motor neurons of the brainstem and spinal cord [65]. Recent studies have shown that these TDP-43–positive inclusions also consist of dipeptide repeat (DPR) proteins, which are the result of the bidirectional translation of the non-coding GGGGCC repeats through a mechanism of non–ATG-initiated translation, called RAN translation (Figure 3) [66,67]. These observations suggest that DPR aggregation due to RAN translation could be the initial pathological event that possibly triggers TDP-43 accumulation in neurons [68]. Despite recent findings implicating both loss-of-function and gain-of-function mechanisms with new insights into the roles of DPR proteins and RAN translation, the relative contribution of these mechanisms and the molecular pathways that lead to neurodegeneration are yet to be elucidated.

CHMP2B

The *CHMP2B* gene, located at chromosome 3p11.2, was identified in 2005 in a large Danish family with an autosomal FTD [23]. The mutation occurs in a splice acceptor site, resulting in the production of two variants of C-terminally truncated CHMP2B proteins. A subsequent study in a Belgian FTD cohort identified a familial FTD patient with a distinct truncation mutation, CHMP-2B^{Q165X}, that leads to the loss of the final 49 amino acids, providing further evidence that C-terminal truncations of CHMP2B lead to FTD [69]. Since then, several studies have found missense mutations in the *CHMP2B* gene that contribute to some families with familial FTD with and without ALS (less than 1%) [70,71]. The presence of *CHMP2B* gene mutations in a small number of families has been reported to be accompanied by parkinsonism features, dystonia, and myoclonus [72]. However, the mutation frequency of the *CHMP2B* gene in patients with FTD and parkinsonism is low (Figure 1). Further studies enrolling more patients are needed to elucidate the role of this gene in parkinsonism syndrome.

The protein encoded by *CHMP2B* is charged multivesicular body (MVB) protein 2B, a subunit of the endosomal sorting complex required for transport (ESCRT)-III, which mediates the bending and fusion of cellular membranes [73]. This membrane manipulation by ESCRT complexes is essential for the maturation of endosomes, which acquire numerous intraluminal vesicles to form late endosomes, or MVBs [73]. MVBs ultimately fuse with lysosomes or autophagosomes to allow degradation of the endosomal content. Mutant CHMP2B protein affects the maturation of both endosomes and autophagosomes (Figure 3) [74,75]. Consistent with these observations, one recent study using transgenic mice with the FTD-causative mutant *CHMP2B* showed that the animals develop a lysosomal storage pathology characterized by large neuronal lysosomal and late-endosomal aggregates, findings also observed on neuropathological assessment in patients carrying *CHMP2B* mutations [76]. Of note, *PGRN*, another FTD-causative gene, and *TMEM106B*, a potential genetic risk factor for FTD, also play a role in regulating endolysosomal and lysosomal functions [45,46,53]. In addition, one recent study showed that the endogenous function of CHMP2B is required for maintaining the stability and complexity of neuronal dendritic spines and trees [77]; the process of dendritic arborization depends on an intact endosomal trafficking system [78]. These findings imply that impaired lysosomal degradation and endosomal trafficking dysfunction are key pathways in FTD associated with the *CHMP2B* mutation.

VCP

The *VCP* gene, located on chromosome 9p13.3, encodes valosin-containing protein. A variant has been identified in North American families with an autosomal dominant multisystem syndrome involving inclusion body myopathy, Paget's disease of the bone, and frontotemporal dementia [79]. The frequency of *VCP* mutations in

FTD is rare, accounting for less than 2% of cases [80]. The disease usually begins at the age of 40 with myopathic symptoms as the initial presentation in the majority of patients, followed by adult-onset Paget disease of bone [79]. FTD, especially bvFTD, ALS, and parkinsonism features, may usually develop later in the disease course. Rarely, *VCP* mutations have been found in patients with a dementia-only phenotype [80] and typical Parkinson's disease with resting tremor and levodopa responsiveness [81].

Valosin-containing protein is one of the ATPases associated with various cellular activities and is involved in multiple cellular processes, including protein degradation via both proteasome and autophagy pathways, membrane fusion, transcriptional activation, apoptosis, and molecular chaperoning (Figure 3) [82]. However, the exact molecular mechanism remains elusive, as does the interaction with other FTD-causing disease proteins in the pathogenesis of FTD with other neurodegenerative systems, including muscles, motor neurons, and the extrapyramidal system.

TARDBP

Mutations in the *TARDBP* gene were initially described in 2008 in patients with ALS, in both familial and sporadic forms [83,84]. The most common phenotype of *TARDBP* mutations is ALS (Figure 2), which accounts for 2-3% of familial ALS patients (Table 1). Some *TARDBP* mutation carriers also uncommonly manifest FTD, especially bvFTD, and Parkinson's disease with some levodopa responsiveness [85,86]. The inheritance mode is autosomal dominant with unclear penetrance.

The *TARDBP*-encoded protein, TDP-43, is a ubiquitously expressed and highly conserved ribonucleoprotein. TDP-43 is postulated to be involved in transcriptional activity, messenger RNA splicing, exon skipping, and microRNA regulation (Figure 2). Studies have found that in neurodegenerative disorders, TDP-43 can be redistributed from the nucleus to the cytoplasm and sequestered into inclusions that consist mainly of abnormally phosphorylated and C-terminally truncated TDP-43 fragments [87,88] .Because TDP-43 inclusions have also been observed in non–TARDBP-associated genetic forms of FTD, including those involving *PGRN*, *VCP*, and *C9orf72* mutations, these findings suggest that dysregulation of TDP-43 might be a common downstream pathogenic pathway in these neurodegenerative disorders.

FUS

FUS, located on chromosome 16, was identified in 2009 in families with ALS and expands the genetic heterogeneity of FTD [89]. *FUS* mutations have also been identified in patients with FTD-motor neuron disease/ALS and are rare (less than 3%) genetic causes of familial cases of FTD and ALS (Table 1 and Figure 2) [90]. Case reports have described a pure FTD phenotype without motor neuron involvement in *FUS* mutation carriers [24,91]. Rare *FUS* mutation carriers present with parkinsonism features [24].

The FUS protein is the most characteristic pathological marker of the tau-negative and/or TDP-43–negative FTLD cases (Figure 1). The FUS protein belongs to the family of DNA/RNA-binding proteins, which are ubiquitously expressed, multifunctional binding proteins involved in various cellular processes, including cell proliferation, DNA repair, transcription regulation, and multiple levels of RNA and microRNA processing (Figure 3) [92]. TDP-43 is also an RNA processing protein, and both FUS and TARDBP dysfunction affect global cellular RNA regulation [87,88,92]. In addition, the recent discovery that expression of the mutant *C9Orf72* gene may induce RNA foci that could sequester RNA binding proteins such as TDP-43 and FUS highlights a further possibly important mechanism of RNA dysfunction in this neurodegenerative spectrum [20]. Furthermore, TDP-43 and FUS could bind and regulate key aggrephagy-related genes whereas dysfunction of aggrephagy leads to cytoplasmic re-localization and aggregation of TDP-43 [93]. VCP protein, another FTD-causative gene product, is linked to aggrephagy and lysosomal degradation pathways, highlighting the interaction between RNA dysfunction and the autophagosome/lysosomal degradation pathway in the disease process.

Conclusion and Future Directions

Clinical, genetic, and pathological heterogeneity are characteristic features of FTD. The clinical phenotypes can include memory impairment, personality changes, and language impairment and are variably associated with parkinsonism features and motor neuron disorders. The neuropathology is also strikingly variable, encompassing FTLD-tau (mostly found in patients carrying *MAPT* mutations), FTLD-TDP (observed in patients carrying *PGRN*, *C9orf72*, *TARDBP*, or *VCP* mutations), FTLD-FUS (mostly found in ALS patients carrying *FUS* mutations), and FTLD-U. In the past decade, considerable progress has been made toward unraveling the genetic causes of FTD with parkinsonism or motor neuron disorders. The most common causative genes for FTD with parkinsonism syndrome are *MAPT*, *PGRN*, and *C9ORF72*, but they are associated with a wide range of phenotypes. Mutations in other genes, including *TARDBP*, *VCP*, *CHMP2B* and *FUS*, although rare genetic causes of familial FTD with overlapping neurodegenerative features, could explain a small number of the remaining familial cases. Numerous attempts have been made to identify an *in vivo* biomarker that can accurately predict the underlying neuropathology and causative variant, but a clear phenotype–genotype pathology association has not yet been established. Alterations in the protein degradation system and RNA processing pathway are pivotal in familial forms of FTD with parkinsonism and/or motor neuron disorders, but the mechanism of neuronal specificity in the frontal–temporal cortex, basal ganglia, and spinal motor neurons remains elusive.

As parkinsonism is a common clinical feature associated with FTD, our current review provides updated information and a better understanding of this disease spectrum. Considering the vast clinical, genetic, and pathological heterogeneity associated with this disease, the development of accurate biomarkers is mandatory for guiding genetic diagnosis and for defining distinctive mechanism-based therapeutic approaches in future clinical trials.

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