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Parkinsonian Syndrome in Familial Frontotemporal Dementia

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Abstract

Parkinsonism in frontotemporal dementia (FTD) was first described in families with mutations in the microtubule-associated protein tau (*MAPT*) and progranulin (*PRGN*) genes. Since then, mutations in several other genes have been identified for FTD with Parkinsonism, including chromosome 9 open reading frame 72 (*C9ORF72*), chromatin modifying protein 2B (*CHMP2B*), valosin-containing protein (*VCP*), fused in sarcoma (*FUS*) and transactive DNA-binding protein (*TARDBP*). The clinical presentation of patients with familial forms of FTD with Parkinsonism is highly variable. The Parkinsonism seen in FTD patients is usually characterized by akinetic-rigid syndrome and is mostly associated with the behavioral variant of FTD (bvFTD); however, some cases may present with classical Parkinson's disease. In other cases, atypical Parkinsonism resembling progressive supranuclear palsy (PSP) or corticobasal syndrome (CBS) has also been described. Although rare, Parkinsonism in FTD may coexist with motor neuron disease. Structural neuroimaging, which is crucial for the diagnosis of FTD, shows characteristic patterns of brain atrophy associated with specific mutations. Structural neuroimaging is not helpful in distinguishing among patients with parkinsonian features. Furthermore, dopaminergic imaging that shows nigrostriatal neurodegeneration in FTD with Parkinsonism cannot discriminate parkinsonian syndromes that arise from different mutations. Generally, Parkinsonism in FTD is levodopa unresponsive, but there have been cases where a temporary benefit has been reported, so dopaminergic treatment is worth trying, especially, when motor and non-motor manifestations can cause significant problems with daily functioning. In this review, we present an update on the clinical and genetic correlations of FTD with Parkinsonism.

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DISCLOSURES/CONFLICTS

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Keywords

Parkinsonism; familial; frontotemporal dementia; genetics; autosomal dominant; mutation; phenotype

1. Introduction

In 1996, an international consensus conference was held in Ann Arbor, MI, USA to discuss the association of Parkinsonism with Frontotemporal dementia (FTD), and the term *Frontotemporal Dementia and Parkinsonism linked to chromosome 17* (FTDP-17) was introduced [1]. At that time, 13 families were described as having FTDP-17 with an autosomal dominant pattern of inheritance. The clinical features of patients in these families were characterized as behavioral changes, dementia, Parkinsonism, amyotrophy, dystonia, and supranuclear gaze palsy.

FTD is clinically characterized by early behavioral changes and/or language impairment, which is followed by cognitive decline and dementia. Parkinsonism is usually present in the behavioral variant of FTD (bvFTD), but it is rarely seen in primary progressive aphasia (PPA), which is a language variant of FTD [2, 3, 4]. Parkinsonism in FTD may present before, during, or after the development of behavioral or language disturbances. The clinical manifestations of the Parkinsonism seen in FTD patients are varied. Parkinsonian syndrome in FTD ranges from an apparent classical presentation of Parkinson's disease (PD) to atypical Parkinsonism that resembles progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) [2].

Up to 40% of FTD patients have a positive family history, which suggests a strong genetic component to these disorders. It is estimated that autosomal dominant cases account for over 13% of the total number of FTD cases [5, 6]. Currently, the best understood forms of autosomal dominant FTD associated with Parkinsonism are those linked to chromosome 17 and related to mutations in the microtubule-associated protein tau (*MAPT*) and progranulin (*PGRN*) genes [7, 8, 9]. Besides *MAPT* and *PGRN*, the chromosome 9 open reading frame 72 (*C9ORF72*) gene, which was identified in 2011 is known to be the major causative gene for familial FTD that is also associated with Parkinsonism [3, 4, 7, 8, 10, 11]. Mutations in four other genes: valosin-containing protein (*VCP*), chromatin modifying protein 2B (*CHMP2B*), transactive DNA-binding protein (*TARDBP*) and fused-in-sarcoma (*FUS*) are identified in a minority of FTD cases accompanied by the parkinsonian phenotype [12, 13, 14, 15]. In this review we describe the clinical features in familial FTD with Parkinsonism with known genetic defect.

2. Clinical genetics, general characteristic, and parkinsonian features in familial FTD with Parkinsonism

Molecular genetic studies in patients with FTD associated with Parkinsonism have identified mutations in several genes: *MAPT*, *PGRN*, *C9ORF72*, *CHMP2B*, and *VCP*. Mutations found in common ALS genes, *TARDBP* and *FUS*, may also contribute to FTD associated with Parkinsonism (Table 1). Parkinsonism seen in FTD patients carrying different autosomal

dominant gene mutations can have a diverse clinical manifestation. In Table 2 we provide a summary of parkinsonian features and other motor and non-motor manifestations that could be present in patients with FTD.

2.1 FTDP-17 (*MAPT*)

Mutations in the *MAPT* account for up to approximately 50% of FTD cases and the majority of FTDP-17 cases. Over 50 pathogenic *MAPT* mutations have been described (www.molgen.ua.ac.be/FTDMutations) [16]. The mode of inheritance is autosomal dominant. The mean age at onset is 49 years, but this can range from 25–76 years. The mean disease duration is approximately 7 years, but could be longer e.g. tau p.R406W mutation carriers can survive into the eighth decade of life [12, 17, 18, 19]. A positive family history is almost always present in *MAPT* mutation carriers, and their penetrance is nearly 100% [20]. No gender predilection has been identified [21]. The clinical presentation of FTDP-17 (*MAPT*) is variable, but cardinal signs include personality and behavioral changes, dementia, and Parkinsonism. At the onset of the disease, only one of these signs is typically exhibited, but in advanced disease stages all of the signs could be present. Based on the type of *MAPT* mutation, the initial FTDP-17 phenotype can be divided into frontotemporal dementia-predominant or Parkinsonism-predominant [22]. However, the most common clinical presentation of FTDP-17 (*MAPT*) is bvFTD. FTDP-17 (*MAPT*) patients experience slowly progressive dementia with gradual functional decline. Motor neuron deficits, such as amyotrophy and fasciculation are rarely seen [23, 24, 25].

2.1.1. Parkinsonism in FTDP-17 (*MAPT*)—Parkinsonism can be the first manifestation of FTDP-17 caused by mutations in *MAPT (FTDP-17 (MAPT))*, and it can initially have a good response to levodopa therapy. Because of this, some patients could be misdiagnosed as having PD at the early stage of the disease. When Parkinsonism is the first symptom of FTDP-17, it is usually caused by mutations in exon 10 of the *MAPT* gene (p.N279K, p.delN296, p.S305S, p.N296N, and p.G303V) [17, 25]. However in some FTDP-17 (*MAPT*) mutations, Parkinsonism occurs late in the disease course (p.P301S and p.N296H), or is rare and minimal (p.P301L, p.S305N, p.S352L, p.G272V, and p.R5L). Parkinsonism seen in FTDP-17 (*MAPT*) patients includes severe limb bradykinesia, axial and limb rigidity, and postural instability. These signs are often symmetric, and there is usually no resting tremor. Postural or action tremor may be observed, but this is rare. Atypical parkinsonian syndromes are also described in association with *MAPT* mutations; these are more likely associated with PSP syndrome than CBS. Parkinsonism accompanied by oculomotor abnormalities is usually present in p.delN296, p.S305S, and p.N279K mutations; these include slowed saccades, supranuclear gaze palsy resembling PSP syndrome. Rarely, CBS with eyelid apraxia may be present in *MAPT* mutations (p.P301S). Parkinsonism in FTDP-17 (*MAPT*) may also be accompanied by bulbar symptoms, including dysarthria and dysphagia, or corticospinal tract involvement, which may present as hyperreflexia, clonus, extensor plantar responses, and dystonia or myoclonus. Patients may occasionally respond to levodopa therapy at the initial stage of their illness; however, that is rarely sustained during the disease course [4, 21, 23, 26]. There is no clear association between cognitive decline and the presence, severity, or onset of Parkinsonism in FTDP-17 (*MAPT*) [20]. In most *MAPT* mutations, motor neuron disease is rarely present; however, p.K317M, p.N296N, and

p.P301L mutations could be associated with amyotrophy, fasciculation, and denervation. The most common *MAPT* mutations associated with parkinsonian features and their clinical presentations are summarized in Table 3.

2.2 FTDP-17 (*PGRN*)

Mutations in the *PGRN* account for approximately 26% of FTD cases. More than 70 pathogenic *PGRN* mutations have been described so far (www.molgen.ua.ac.be/FTDMutations). The mode of inheritance is autosomal dominant. The mean age at onset is around 59 years, almost a decade later than that of FTDP-17 (*MAPT*) cases, but it can range from 48–83 years [3]. The disease duration is variable and ranges from 1–14 years and is usually shorter on average than that of *MAPT* mutation carriers. *PGRN* mutations show age-dependent penetrance. The penetrance reaches 90% at age 70 years [27, 28, 29, 30]. A wide spectrum of cognitive, behavioral, and motor features in FTDP-17 is associated with *PGRN* mutations, but the particular type of mutation does not predict the clinical syndrome [27, 28, 29, 31, 32]. *PGRN* mutations are usually associated with bvFTD, but unlike *MAPT* mutation carriers, an isolated language dysfunction and primary progressive aphasia syndrome (PPA) can be also observed [3]. A careful language evaluation may help to predict *PGRN* mutations in FTDP patients [21]. Measurement of serum progranulin levels, which are extremely low in *PGRN* mutation carriers, may help achieve a correct diagnosis in FTDP-17 independently of the phenotypic presentation when genetic testing is unavailable. It has been suggested that this approach could be used as a cost-effective prediction of *PGRN* mutations among FTDP-17 patients [33, 34].

2.2.1. Parkinsonism in FTDP-17 (*PGRN*)—Mild Parkinsonism characterized by akinetic-rigid syndrome occurs relatively frequently (40–60%) in patients with *PGRN* mutations, but this is usually late in the disease course and occurs after the development of FTD phenotype [9]. In minority of the cases carrying *PGRN* mutations (p.Leu271LeufsX10), Parkinsonism has been described as a predominant clinical manifestation [4]. Some FTDP-17 cases with *PGRN* mutations present both visual hallucinations and Parkinsonism, which is suggestive of Lewy body disease [21, 35]. Some cases may have atypical parkinsonian features characterized by progressive asymmetric rigidity and apraxia, which is reminiscent of CBS (p.V200GfsX18, p.A9D and p.E498DfsX12) [36]. Asymmetric apraxia that is consistent with parietal lobe dysfunction and is associated with parkinsonian signs that present early in the disease course may help distinguish *PGRN* mutation carriers from other FTD patients with parkinsonian syndromes. *PGRN* mutations are suggested to be one of the most common causes of familial CBS [37]. Parkinsonism seen in FTDP-17 (*PGRN*) cases may initially respond to levodopa; however, in most cases, it is not levodopa-sensitive [38, 39]. The specific *PGRN* mutations in which Parkinsonism are most likely to be observed are summarized in Table 4.

2.3 *C9ORF72* expansion

The *C9ORF72* expansion accounts for up to approximately 48% of FTD cases. The *C9ORF72* gene located on chromosome 9 encodes the chromosome 9 open reading frame 72 protein. Abnormal expansions of a noncoding GGGGCC hexanucleotide repeat (700 – 1600 repeats) causes variable combination of clinilcal phenotypes. The *C9ORF72* expansion

length in specific brain regions from autopsy cases with FTD and ALS revealed an association with age at onset in the frontal cortex and disease duration in the cerebellum, but a similar association was not detected in blood [40]. It is not yet known whether the *C9ORF72* expansion length contributes to the different phenotypes associated with the disease thus further studies are needed. The mode of inheritance is autosomal dominant. Anticipation was observed in some families. The age at onset and disease duration is highly variable. The mean age at onset is around 55 years (range 33–75 years). The mean disease duration is approximately 4.5 years, and typically ranges from 3–10 years [41, 42]. The clinical phenotype of *C9ORF72* expansion carriers mainly consists of bvFTD, ALS, or FTD with motor neuron disease.

2.3.1. Parkinsonism in *C9ORF72* expansion—Parkinsonism is reported in about one third of patients with *C9ORF72* expansions [42, 43]. Parkinsonism in FTD due to *C9ORF72* repeat expansions is usually characterized by a relatively symmetric akinetic-rigid syndrome and gait disturbances. Postural and action tremors can occasionally be observed, but resting tremors are typically not seen [41, 44]. Parkinsonism is usually associated with predominant bvFTD or FTD/ALS, but was not described in patients with pure ALS [45, 46]. Parkinsonism in *C9ORF72* FTD patients may remain pure, without associated cognitive deficits or dementia for over 10 years, but this is rare [46, 47]. Cases that present with CBS or PSP syndromes have also been described [48]. Parkinsonian features in patients with *C9ORF72* mutations typically evolve within the first years of the disease course, and can temporarily be levodopa responsive, but most patients do not benefit from anti-parkinsonian treatment [34, 49].

2.4 FTD-3 (*CHMP2B)*

In 2005, the *CHMP2B* gene, located on chromosome 3p11.2, was associated with FTD linked to chromosome 3 (FTD-3) in large kindred from Denmark and one unrelated Belgian familial FTLD patient [37]. The *CHMP2B* gene mutations are currently understood to be a rare genetic cause of familial FTD; only four pathogenic mutations have been described (www.molgen.ua.ac.be/FTDMutations). The mode of inheritance is autosomal dominant. Since the disease has a subtle onset and often slow progression, the exact age at onset can be difficult to determine. The mean age at onset has been reported to be around 58 years, and the mean disease duration is approximately 10 years with great variability [50]. *CHMP2B* mutation carriers typically present with bvFTD at an early stage of their disease, but patients can develop more global loss of cognition [51]. Infrequently, bvFTD can be accompanied by motor symptoms, including parkinsonian features, dystonia, pyramidal signs, and myoclonus; this is especially true in the later stages of the disease [52].

2.4.1. Parkinsonism in FTD-3 (*CHMP2B)*—bvFTD in FTD-3 can be accompanied by motor symptoms, which include parkinsonian features, dystonia, pyramidal signs and myoclonus, but this finding is infrequent or is found late in the disease course [52]. Classical Parkinsonism is seen in a minority of patients carrying *CHMP2B* mutations, and it is usually characterized by asymmetrical akinetic-rigid syndrome [51, 53]. Parkinsonism in FTD-3 typically occurs a few years after the symptomatic disease onset. Rarely, an atypical

parkinsonian phenotype that is accompanied by supranuclear gaze palsy or apraxia could be observed in FTD-3. Responsiveness to levodopa therapy has not been reported.

2.5 *VCP* mutations

The *VCP* gene is located on chromosome 9p13.3 and encodes valosin-containing protein. In 2004, a mutation in *VCP* was found in a rare autosomal dominant multisystem degenerative disorder, inclusion body myopathy and Paget's disease of the bone and frontotemporal dementia (IBMPFD) [54]. Over 15 potentially pathogenic mutations in *VCP* have been described to date. The phenotypic presentations within families with *VCP* mutations are highly variable; about 35% of patients present with personality and cognitive changes. *VCP* mutation phenotypes may also include motor neuron degeneration in the form of familial ALS [42]. Several affected individuals from families with IBMPFD and *VCP* mutations have been reported to manifest with Parkinsonism, especially in the late disease stages [55, 56, 57, 58, 59].

2.5.1. Parkinsonism in *VCP* mutations—Several affected individuals from families with IBMPFD and *VCP* mutations (p.R159C, p.R191Q, p.T262A, and p.P137L) have been reported to manifest with akinetic-rigid Parkinsonism that usually presents in the late disease stages [55, 56, 58, 59]. Single cases with an p.R159C mutation in the *VCP* have been reported with typical PD features including resting tremor, REM sleep behavioral disorder (RBD), and lasting levodopa responsiveness [54, 60, 61]. However, *VCP* is rarely associated with Parkinsonism [54].

2.6 *TARDBP* mutations

In 2008, the *TARDBP* gene mutation was identified as a causative gene for ALS. The *TARDBP* gene, located on chromosome 1p36.22, encodes a 43-kDa ubiquitously expressed nuclear DNA- and RNA-binding protein (TDP-43) [62]. To date, more than 30 *TARDBP* mutations have been reported, which explains approximately 4% of familial ALS cases and a smaller proportion of FTD cases [63]. The mode of inheritance is autosomal dominant. The most common clinical phenotype associated with *TARDBP* mutations is ALS. Several patients carrying *TARDBP* mutations have been reported to develop Parkinsonism [62, 63, 64].

2.6.1. Parkinsonism in *TARDBP* mutations—Several patients carrying *TARDBP* mutations have been reported to develop Parkinsonism in addition to the FTD phenotype [63, 64, 65]. An A382T mutation was described to be associated with a typical PD phenotype or FTD with levodopa-responsive Parkinsonism in the absence of cognitive or motoneuron disturbances [10]. Other mutation carriers presented with a combination of Parkinsonism and ALS and/or FTD. Parkinsonism due to *TARDBP* mutations is characterized as a mixed type with predominant akinetic-rigid syndrome and may be accompanied by dystonia or tics. RBD was also reported in *TARDBP* mutation carriers with parkinsonian features. Responsiveness to levodopa therapy is typically good.

2.7 *FUS* mutations

In 2009, mutations in the *FUS* gene were originally described in familial ALS. Mutations in the *FUS* account for up to 4% of familial ALS cases [66]. The *FUS*, located on chromosome 16p11.2., encodes fused in sarcoma protein [67, 68]. A number of specific mutations in *FUS* have been suggested to cause FTD and essential tremor [69, 70]. In a cohort of 476 familial ALS and 41 sporadic ALS cases, a family with the FUS p.R521C mutation was identified in the proband, who developed ALS with Parkinsonism and dementia.

2.7.1. Parkinsonism in *FUS* mutations—A single case of a patient with a p.M254V mutation that was associated with bvFTD and parkinsonian signs that developed further in the disease course has been reported [15]. The Parkinsonism in this case was characterized by rigidity; however, information about other motor and non-motor manifestations and responsiveness to levodopa was not provided. So far, very little is known about FTD with Parkinsonism due to *FUS* mutations.

Clinical characteristic of C9ORF72, CHMP2B, TARDBP, VCP and FUS genes mutations associated with Parkinsonism in FTD are summarized in Table 5.

3. Neuroimaging in FTD with Parkinsonism

Structural neuroimaging (MRI) is essential to the evaluation of patients with FTD, and characteristic patterns of brain atrophy are associated with specific genetic mutations (Table 6). FTDP-17 (*MAPT*) typically shows symmetrical fronto-temporal lobe atrophy, with the most severe abnormalities observed in the temporal lobes, whereas highly asymmetrical fronto-parieto-temporal atrophy is seen in FTDP-17 (*PGRN*) [71, 72, 73]. If symmetrical fronto-temporal atrophy is associated with midbrain atrophy, usually similar extrapyramidal features to those seen in PSP syndrome are observed. The presence of early parietal lobe atrophy in *PGRN* mutations may help to distinguish such cases from other patients with parkinsonian features in FTD. *PGRN* mutations are also associated with faster rates of whole brain atrophy compared to *MAPT* mutations [73]. It has been demonstrated that apart from fronto-temporal pathology, atrophy in the occipital lobes and cerebellum can help differentiate subjects with *C9ORF72* mutations from those with *MAPT* or *PGRN* mutations or sporadic disease [10, 11, 34, 43]. Structural neuroimaging studies of patients with *CHMP2B*, *TARDBP*, *VCP*, and *FUS* mutations do not show specific patterns of brain atrophy, but atrophy that is usually spread throughout the frontal, temporal, and parietal lobes [12, 74, 75, 76].

Structural neuroimaging cannot help distinguish between FTD cases with and without parkinsonian features. Furthermore, in patients showing clear brain atrophy on MRI, little additional diagnostic benefit is gained by doing single photon emission computed tomography (SPECT) or positron emission tomography (PET) scans because hypoperfusion and hypometabolism are usually present in the same regions where MRI shows atrophy [77]. However, in patients with Parkinsonism in FTD, perfusion SPECT with ^{99}Technet-ethylene cystine dimer (^{99}Tc-ECD-SPECT) or ^{18}F-fluorodeoxyglucose PET (FDG-PET) may confirm the extrapyramidal system dysfunction by showing reduced cerebral blood flow (^{99}Tc-ECD-SPECT) and hypometabolism (FDG-PET) in the basal ganglia [78, 79, 80, 81].

Functional imaging with specific dopamine-related tracers (e.g. ^{99m}Tc-TRODAT-1, ^{123}I-β-CIT, and ^{123}I-FP-CIT for SPECT, and ^{18}F-DOPA, ^{11}C-DOPA, and ^{11}C-raclopride for PET) may assist in confirming the nigrostriatal neurodegeneration seen in various parkinsonian syndromes including FTD with Parkinsonism and may be used to discriminate between neurodegenerative Parkinsonism and its mimics e.g. drug-induced Parkinsonism [78]. In FTD patients, where neuroleptics are widely used to assist with behavior disorders, it is important to differentiate between Parkinsonism with underlying neurodegenerative pathology and a drug-induced syndrome. The uptake of tracer is normal in drug-induced Parkinsonism, and an abnormal image supports the diagnosis of dopaminergic system neurodegeneration [82]. Unfortunately, neuroimaging of the dopaminergic system has cannot differentiate between PD and atypical Parkinsonism well [77]. Furthermore, dopaminergic imaging is not helpful in discrimination between different atypical parkinsonian syndromes, including FTD with Parkinsonism [83].

4. Pathologic findings in FTD with Parkinsonism

Neuropathologically, FTD is defined as *Frontotemporal Lobar Degeneration* (FTLD), a proteinopathy characterized by the presence of abnormal protein inclusions in the cytoplasm or nuclei of neuronal and glial cells. Parkinsonian features in FTD are most likely associated with tau pathology (FTLD-tau). *MAPT* mutation carriers with Parkinsonism in FTD exhibit a combination of tau-immunoreactive aggregates in neurons, astrocytes, and oligodendroglial cells that are localized in the cortex, basal ganglia, and the subcortical white matter [68]. However, more than 50% of FTLD patients present with tau-negative, TDP-43–positive ubiquitinated neuronal and glial cytoplasmic inclusions (FTLD-TDP). TDP-43–positive inclusions are the pathological hallmark in FTD with Parkinsonism caused by *PGRN*, *C9ORF72*, *TARDBP*, and *VCP* mutations. *FUS* mutation carriers have FUS-positive, and TDP-43-negative inclusions and are thus referred to as FTLD-FUS. In *CHMP2B* mutation carriers the inclusion protein remains unknown; they exhibit ubiquitin-positive but tau negative inclusions and TDP-43-negative and FUS-negative cytoplasmic inclusions, which are referred to as FTLD-ubiquitin proteasome system (FTLD-UPS), previously known as FTLD-ubiquitin (FTLD-U) [84].

5. Differential diagnosis of Parkinsonism in FTD

The main considerations in the differential diagnosis of Parkinsonism in FTD are other neurodegenerative diseases. Parkinsonism in FTD is present in addition to behavioral and personality changes and usually occurs a few years after the cardinal FTD symptoms are present.

The atypical Parkinsonism with oculomotor disturbances and severe postural instability that cause frequent falls and are characteristic for PSP can occur in the disease course of autosomal dominant genes mutations in FTD with Parkinsonism. The same is true for the asymmetrical parkinsonian syndrome with additional motor and non-motor manifestations such as myoclonus and dystonia followed by focal cortical deficits, which are characteristic for CBS. Conversely to sporadic disease, the PSP and CBS phenotypes associated with FTD with Parkinsonism usually develop after the behavioral and personality changes that are

characteristic for bvFTD. MSA is mostly sporadic, progressive neurodegenerative disease, but it is unlike FTD with Parkinsonism where half of the patients report positive family history. Furthermore, the Parkinsonism found in MSA is associated with severe autonomic failure, cerebellar ataxia, and corticospinal disorders, which are not seen in FTD. The main differences between FTD with Parkinsonism and DLB are the rare visual hallucinations of FTD and the dominant dementia and fluctuations in cognitive status present in DLB. Finally, the clinical presentations that are the hallmark of typical PD are rarely seen in FTD patients with Parkinsonism. The presence of additional symptoms that are characteristic for bvFTD and the lack of levodopa response in most cases should help differentiate FTD with Parkinsonism from classical PD.

6. Management of Parkinsonism in FTD

Most patients with Parkinsonism in FTD respond poorly to levodopa (Tab.2). There are no data on the use of dopamine agonists in Parkinsonism in FTD. Furthermore, dopaminergic agents may trigger or exacerbate the psychiatric disturbances present in FTD such as agitation, delusions, paranoia, and hallucinations. Therefore, Parkinsonism in FTD should be treated if it creates significant problems with daily functioning. Using anti-parkinsonian agents requires empiric testing of tolerability and efficacy [84]. In the absence of pharmacological treatment, physical therapy can be helpful to preserve mobility, to reduce risk of falls, and to extend independence in activities of daily living [85].

7. Conclusion

In this review, we have summarized the current knowledge on the clinical and genetic correlations of FTD with Parkinsonism. It has become clear over the last two decades that there are multiple genetic autosomal dominant mutations leading to the development of FTD associated with Parkinsonism. The most common causative genes are *MAPT*, *PGRN*, and *C9ORF72*, but they are associated with a wide range of phenotypes. Substantial evidence supports the concept that FTD shares overlapping clinical features with other neurodegenerative disorders. Parkinsonism in FTD may present as classic PD (albeit rarely and usually early in the course of the illness); and if so it is characterized by an akinetic-rigid syndrome. In this rare situation it rather quickly evolves to the atypical Parkinsonism with lack of responsiveness to levodopa. In most cases Parkinsonism even from its onset is of atypical nature resembling phenotypes of PSP or CBS. Neuroimaging studies show characteristic patterns of brain atrophy for different gene mutations, but are not very helpful for the diagnosis of Parkinsonism in FTD. A precise diagnosis is made through a genetic testing. However, there are still a number of cases presenting with an FTD with parkinsonian phenotype, but without known genetic cause.

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Highlights

- FTD with Parkinsonism is frequently caused by mutations in MAPT, PGRN, and C9ORF72 genes
- Parkinsonism in FTD may initially present as classical PD
- Some cases may benefit from levodopa but most do not
- Symptoms vary and may resemble PSP and corticobasal syndrome.
- MRI, PET, and SPECT cannot discriminate among syndromes arising from different mutations

Table 1

The profile of genes associated with Parkinsonism in FTD

		MAPT	PGRN	C9ORF72	CHMP2B	TARDBP	VCP	FUS
Chromosomal localization		17q21.32	17q.21.31	9p21.2	3p11.2	1p36.22	9p13.3	16p11.2
Inheritance		AD	AD	AD	AD	AD	AD	AD
Penetrance		Almost 100%	90% by 70 years	Probably high	UKN	UKN	Incomplete	UKN
Anticipation		0	+	++	UKN	UKN	UKN	UKN
Estimated mutation frequency in FTD		0–50%	3–26%	14–48%	<1%	<1%	<1%	<1%
Mean AAO (range)		49 years (25–76)	59 years (48–83)	55 years (33–75)	58 years (46–65)	54 years (40–69)	55 years (46–79)	43 years (30–60)
Mean DD (range)		7 years (2–30)	7 years (1–14)	4.5 years (3–10)	10 years (5–21)	3 years (1–5)	6 years (5–8)	3 years (3–7)
Most frequent initial Dx.		bvFTD ±P	bvFTD ±P	FTD/ALS	ALS, FTD	ALS, bvFTD	IBMPFD	FTD, ALS
Clinical Dx. during the disease course	**Most frequent Dx.**	FTD *Parkinsonism*	FTD CBS	FTD MND*	FTD Dementia	MND*	FTD MND*	FTD MND*
	Relatively common Dx.	Pyramidal signs PSP	*Parkinsonism* Pyramidal signs	*Parkinsonism*	*Parkinsonism*	FTD *Parkinsonism*	Dementia	Dementia
	Rare Dx.	CBS MND	MND Hallucinations	CBS	MND* Epilepsy	Dementia	Language impairment *Parkinsonism*	*Parkinsonism*
Prominent neuropathology		Tau	TDP-43	TDP-43, U	U	TDP-43	TDP-43	FUS

AAO=age at onset; AD=autosomal dominant; ALS=amyotrophic lateral sclerosis; bvFTD=behavioral variant frontotemporal dementia; DD=disease duration; Dx.=diagnosis; FTD=frontotemporal dementia; FUS=fused in sarcoma; IBMPFD= inclusion body myopathy and Paget's disease of the bone and frontotemporal dementia; P=Parkinsonism; TDP-43=transactive DNA-binding protein; U=ubiquitin; UKN=unknown; 0=not present; (+)=present in some cases; (++)= frequent;

* includes upper and lower motor neuron deficits.

Table 2

Summary of characteristics of Parkinsonism and motor and non-motor manifestations other movement disorders seen in patients carrying autosomal dominant genes mutations for FTD associated with Parkinsonism

	MAPT	PGRN	C9ORF72	CHMP2B	TARDBP	VCP	FUS
Parkinsonism							
Bradykinesia	+++	+++	++	+	++	++	++
Rigidity	+++	+++	++	++	++	+	+
Postural instability	++	++	+	−	−	−	−
Resting tremor	+/−	+/−	+/−	−	+	+/−	−
Gait impairment	+	+	+	+	−		−
PSP phenotype							
Supranuclear gaze palsy	++	+	+	+	−	−	+
Difficulty initiating saccades	++	+	+	+	−	−	+
CBS phenotype							
Apraxia	+	++	+	++	−	++	+
Cortical sensory loss	−	+	+	−	−	−	−
Alien limb phenomenon	−	+	+	−	−	−	+
Other movement disorders							
Tremor (except resting tremor)	+/−	−	−	−	−	−	−
Dyskinesia	−	−	−	+	−	+	−
Dystonia	−	+	+	+	+	+	−
Myoclonus	+	+	−	+	−	+	−
Chorea	−	−	−	−	−	−	+/−
Tics	−	−	−	−	+	−	−
RBD	−	−	−	−	+	+/−	−
Restless legs syndrome	−	−	−	−	−	−	−
Asymmetry	−	++	+	−	+	−	−
Levodopa responsiveness							
	Might be temporarily effective	Usually not effective	Might be temporarily effective	UKN	Effective	Might be effective	UKN

CBS=corticobasal syndrome; PSP=progressive supranuclear palsy; RBD=REM behavioral sleep disorder; UKN=unknown; (−)=not present/not assessed; (+/−) =infrequent; (+)=present in some cases; (++)=moderate frequency; (+++)=very frequent

Table 3

The *MAPT* mutations in FTDP-17 and their characteristic clinical phenotype.

Gene	***MAPT***										
Amino acid change	**N279K**	**delN296**	**S305S**	**N296N**	**G303V**	**P301S**	**N296H**	**K317M**	**P301L**	**S305N**	**G272V**
Mutation type	Point	Delision	Silent	Silent	Point	Point	Point	Point	Point	Point	Point
Genomic region	Exon 10	Exon 10	Exon 10	Exon 10	Exon 10	Exon 10	Exon 10	Exon 11	Exon 10	Exon 10	Exon 9
AAO (years)	41–50	31–40	>50	>50	31–40	≤30	>50	41–50	41–50	31–40	41–50
DD (years)	6–10	≤5	6–10	6–10	≤5	6–10	≤5	6–10	6–10	≤5	6–10
Early Parkinsonism	+++	+++	+++	+++	+++	−	−	+++	−	−	−
Late Parkinsonism	−	−	−	−	−	+++	+++	−	−	−	−
Rare Parkinsonism	−	−	−	−	−	−	−	−	+	+	+
Personality changes	−	−	+++	−	−	+++	++	−	+++	+++	+++
Dementia	+	+++	+++	−	+	+++	−	+	+++	+++	+++
Language difficulties	+	−	+	+	+	+	++	+	+	+	+
Supranuclear gaze palsy	+	+	+	+	+	+	+	+	−	+	−
Apraxia	+	−	−	+	−	+	−	+	−	+	−
Pyramidal signs	+	−	+	+	+	+	−	−	−	+	−
Amyotrophy	−	−	−	+	−	−	−	+	+	−	−

AAO = age at onset; DD = disease duration; (−) = not present/not assessed; (+) = rare; (++) = present in some cases; (+++) = frequent

Table 4

The *PGRN* mutations in FTDP-17 and their characteristic clinical phenotype.

Gene	***PGRN***								
Aminio acid change	**R493X**	**T304LfsX58**	**C253X**	**A9D**	**T7A**	**G401X**	**E498DfsX12**	**L271LfsX10**	**V200GfsX18**
Mutation type	Point	Insertion	Deletion	Point	Point	Point	Deletion	Deletion	Point
Genomic region	Exon 12	Exon 9	Exon 8	Exon 2	Exon 2	Exon 11	Exon 12	Exon 7	Intron 7
AAO (years)	44–62	57	60	46–59	50	55–69	NA	66	62
DD (years)	3–9	5	NA	4–7	NA	NA	NA	1–8	9
Parkinsonism	++	+	+	+	+	+	+	+++	+
Personality changes	+	+	++	+	+	++	+	++	+
Dementia	+	+	+	+	+	+	+	+	+
Language difficulties	++	+	−	+	−	+	+	+	−
Supranuclear gaze palsy	−	−	−	++	−	−	−	−	−
Apraxia	+	+	−	++	+	+	++	++	++
Pyramidal signs	−	+	−	−	−	−	−	−	−
Amyotrophy	−	−	−	+	−	−	−	−	−

AAO = age at onset; DD = disease duration; NA = not present/not assessed; (−) = absent; (+) = rare; (++) = present in some cases; (+++) = frequent

Table 5

Specific mutations associated with Parkinsonism in FTD and their characteristic clinical phenotype.

Gene	***C9ORF72***	***CHMP2B***	***TARDBP***				***VCP***						***FUS***	
Amino acid change	**NA**	***N143S****	**A382T**	***K263E***	**N267S**	**A315E**	**R159C**	**R191Q**	**T262A**	**P137L**	**R191G**	**R159C**	***M254V****	**R521C**
Mutation type	G_4C_2 hexanucleotide repeat expansion	Point	Point	Point	Point	Point	Point	Point	Point	Point	Point	Point	Point	Point
Genomic region	NA	Exon 5	Exon 6	Exon 6	Exon 6	Exon 6	Exon 5	Exon 5	Exon 5	Exon 4	Exon 5	Exon 5	Exon 6	Exon 15
AAO (years)	58.0	71	53	35	69–74	57–63	53–62	37–63	51–56	38–50	42–45	50–73	52	NA
DD (years)	5.3	9	4	2	NA	4–6	1–5	1–7	4–15	10–21	9	5	NA	NA
Parkinsonism	++	+	+++	+	+	+	+	+	+	+	++	+	+	+
Personality changes	+++	+	+	+	++	−	+	+	+	+	−	+	+	−
Dementia	+	+	+	+	+	−	+	+	++	−	−	+	+	+
Language difficulties	−	+	−	−	+	−	+	+	++	−	−	+	−	−
Supranuclear gaze palsy	−	−	−	+	−	−	−	−	−	−	−	−	−	−
Apraxia	−	+	−	−	−	−	−	−	−	−	−	+	−	−
Pyramidal signs	+	+	−	−	−		++	+++	+	−	+++	−	−	++
Amyotrophy	++	−	+	−	−	+	+++	+++	++	++	+++	+	−	+++

AAO = age at onset; DD = disease duration; NA = not present/not assessed; Sub = substitution; (−) = absent; (+) = rare; (++) = present in some cases; (+++) = frequent;

*not proven to be pathogenic; only one mutations carrier has been identified for each mutation written in Italics.

Table 6

Pattern of changes of neuroimaging in genetic forms of FTD associated with Parkinsonism (findings from structural and functional studies)

	MAPT	PGRN	C9ORF72	CHMP2B*	TARDBP*	VCP*	FUS*
Asymmetry	+/−	+++	+/−	+	+	+	+
Atrophy seen in structural neuroimaging studies (CT/MRI)							
Frontal lobe	+++	++	+++	+	++	+	+
Temporal lobe	+++	++	++	+	−	+	+
Parietal lobe	+	+++	+	+	+	+	−
Other regions	−	Basal ganglia	Occipital lobe, Thalamus Cerebellum	−	Midbrain	−	Caudate nucleus
Hypometabolism seen in ^{18}FDG-PET							
Frontal lobe	+	++	++	++	++	++	+
Temporal lobe	++	++	++	+	+	++	+
Parietal lobe	+/−	+++	+	++	+	+	−
Other regions	Putamen, striatum	−	−	−	Caudate nucleus	−	−
Hypoperfusion seen in ^{99}Tc-ECD-SPECT							
Frontal lobe	++	++	++	NA	++	++	NA
Temporal lobe	++	+	++	NA	+	++	NA
Parietal lobe	+	++	+	NA	−	+	NA
Other regions	−	Hippocampus, Cingulate cortex	−	−	Caudate nucleus, Putamen	Cerebellum	−

CT=computed tomography; MRI=magnetic resonance imaging; ^{18}FDG-PET=^{18}F-fluorodeoxyglucose positron emission tomography; ^{99}Tc-ECD-SPECT=^{99}Technet-ethylene cystine dimer single photon emission tomography;

*Limited information; (−)= not present; (+/−)= infrequent; (+)= present in some cases; (++)= moderate frequency; (+++)= very frequent; NA=not assessed