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Editor's comment: Familial frontotemporal dementia with parkinsonism is one of those disorders that occurs frequently enough that movement disorders specialists know they should be familiar with it, but infrequently enough that it is difficult to remember it, particularly in light of its complexities. Therefore, this review by Siuda and colleagues is an especially informative refresher that provides a cogent, succinct exposition of the clinical presentation of the various mutations, not just on the more familiar chromosome 17, but also on chromosomes 1, 3, 9 and 16, that produce the disorder. In addition to detailing the clinical presentation of the various mutations, the authors describe the neuroimaging characteristics, delineate the pathologic findings and discuss the differential diagnosis and treatment of this important disorder.

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Review

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.

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

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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 [2–4]. Parkinsonism in FTD may present before, during, or after the development of behavioral or language disturbances. The clinical manifestations of 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 [7–9]. 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 [10,11]. Mutations in four other genes: chromatin modifying protein 2B (*CHMP2B*), valosin-containing protein (*VCP*), transactive DNA-binding protein (*TARDBP*), and fused-in-sarcoma (*FUS*) are identified in a minority of FTD cases accompanied by the parkinsonian phenotype [12–15]. 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 to 76 years. The mean disease duration is approximately 7 years, but the disease duration could be longer; for example, tau p.R406W mutation carriers can survive into the eighth decade of life [12,17–19]. 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 [23–25].

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 and p.G272V). 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

Table 1
The profile of genes associated with parkinsonism in FTD.

		MAPT	*PGRN*	*C9ORF72*	*CHMP2B*	*VCP*	*TARDBP*	*FUS*
Chromosomal localization		17q21.32	17q.21.31	9p21.2	3p11.2	9p13.3	1p36.22	16p11.2
Inheritance		AD	AD	AD	AD	AD	AD	AD
Penetrance		Almost 100%	90% by 70 years	Probably high	UKN	Incomplete	UKN	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 (44–83)	55 years (33–75)	58 years (46–71)	55 years (37–79)	54 years (35–74)	43 years (30–60)
Mean DD (range)		7 years (2–30)	7 years (1–14)	4.5 years (3–10)	10 years (5–21)	6 years (1–21)	3 years (1–6)	3 years (3–7)
Most frequent initial Dx.		bvFTD ± P	bvFTD ± P	FTD/ALS	ALS, FTD	IBMPFD	ALS, bvFTD	FTD, ALS
Clinical Dx. during the disease course	Most frequent Dx.	FTD	FTD	FTD	FTD	FTD	MND[a]	FTD
		Parkinsonism	CBS	MND[a]	Dementia	MND[a]		MND[a]
	Relatively common Dx.	Pyramidal signs	*Parkinsonism*	*Parkinsonism*	*Parkinsonism*	Dementia	FTD	Dementia
		PSP	Pyramidal signs				*Parkinsonism*	
	Rare Dx.	CBS	MDS[a]	CBS	MND[a]	Language impairment	Dementia	*Parkinsonism*
		MDS[a]	Hallucinations		Epilepsy	*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.

[a] Includes upper and lower motor neuron deficits.