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Clinical Aspects of Familial Forms of Frontotemporal Dementia Associated with Parkinsonism

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Abstract

Frontotemporal dementia is the second most common dementia among people under the age of 65. Fifty percent of affected patients have an associated family history. Several pathogenic genes have been identified for frontotemporal dementia associated with parkinsonism, including microtubule-associated protein tau, progranulin, and chromatin modifying protein 2B, and fused in sarcoma. It has also been reported that frontotemporal dementia associated with parkinsonism can be linked to chromosome 9p. In addition, there are families with frontotemporal dementia associated with a parkinsonian phenotype but unknown genetic status. Some of these kindreds have been diagnosed clinically as familial progressive supranuclear palsy, hereditary diffuse leukoencephalopathy with axonal spheroids, “overlap” syndrome, and others. Clinical presentation of frontotemporal dementia associated with parkinsonism is variable at age of symptomatic disease onset, disease duration, symptoms, and their occurrence during the disease course. Clinically, it is often difficult to sort out the different genetic forms of frontotemporal dementia associated with parkinsonism. However, with available clinical genetic testing for known genes, the precise diagnosis can be accomplished in some cases.

Keywords

Familial; Frontotemporal dementia; Parkinsonism; *MAPT*; *PGRN*; 9p-linked

Introduction

Our understanding of clinical and genetic aspects of frontotemporal dementia (FTD) has been significantly expanded over the last two decades. Approximately 35% to 50% of FTD patients have positive history of family members affected by FTD or other neurodegenerative disorders (Chow et al. 1999). Several genes and a genetic locus have been identified. In our review, we discuss the phenotypic characteristics of these rare familial forms of FTD associated with parkinsonism (FTDP) including those with known genetic defects and those with unknown genes.

Familial FTDP with Known Genes

There are two pathogenic genes located on chromosome 17 associated with FTDP phenotype, microtubule-associated protein tau (*MAPT*), which causes frontotemporal dementia with parkinsonism linked to chromosome 17 with tau pathology (FTDP-17T/*MAPT*), and progranulin (*PGRN*), which causes frontotemporal dementia with parkinsonism

linked to chromosome 17 with ubiquitin pathology (FTDP-17U/*PGRN*). The other pathogenic genes include chromatin modifying protein 2B (*CHMP2B*) causing FTD on chromosome 3 (FTD-3/*CHMP2B*), and fused in sarcoma (*FUS*) on chromosome 16 causing amyotrophic lateral sclerosis (ALS) with FTD (ALS-FTD/*FUS*). These last two genes only rarely produce FTDP phenotype. In addition, valosin-containing protein (VCP) gene causes FTD but without associated parkinsonism as far as it can be determined at the time of our writing. Therefore, it is not included in our review. It should be mentioned that all these diseases are rare and much more needs to be learned about clinical phenotypes and particularly clinical–genetic phenotypic correlations.

FTDP-17T/*MAPT* and FTDP-17U/*PGRN*

Since the original discovery of *MAPT* gene in 1998 (Hutton et al. 1998; Poorkaj et al. 1998; Spillantini et al. 1998), 44 different pathogenic mutations have been identified. *PGRN* gene, which was discovered in 2006 (Baker et al. 2006; Cruts et al. 2006), has at the present time 68 pathogenic mutations that have been identified (current listing of *MAPT* and *PGRN* mutations is available at <http://www.molgen.ua.ac.be/FTDMutations>) (AD&FTD Mutation Database 2011). Both genes are located on chromosome 17q21 approximately 1.7 Mb apart (*PGRN* is more centromeric to *MAPT*). The mode of inheritance for FTDP-17T/*MAPT* and FTDP-17U/*PGRN* is autosomal dominant. The pathological characteristic of FTDP-17T/*MAPT* is tau-positive neuronal and glial inclusions. On the other hand, pathology of FTDP-17U/*PGRN* is dominated by tau-negative but ubiquitin-positive neuronal inclusions that are also TDP-43 positive. The clinical features of FTDP-17T/*MAPT* and FTDP-17U/*PGRN* are summarized in Table 1. The mean age of symptomatic disease onset for both, FTDP-17T/*MAPT* and FTDP-17U/*PGRN*, is younger than for common forms of dementia such as Alzheimer's disease. However, FTDP-17T/*MAPT* symptomatic disease onset is about a decade earlier than for FTDP-17U/*PGRN*. The mean disease duration is similar, about 7 years. Both conditions usually present with behavioral and personality changes followed by dementia, but parkinsonism is more common in FTDP-17T/*MAPT*. Parkinsonism can even be a presenting clinical feature in FTDP-17T/*MAPT*. Parkinsonism is characterized by rigidity and bradykinesia with paucity of rest tremor (occasionally rest tremor can be seen particularly early in disease course). Levodopa therapy can be initially beneficial, but a sustained response is rarely present. Responsiveness to levodopa is more frequent in cases with FTDP-17T/*MAPT*.

FTD-3/*CHMP2B*

Gydesen and colleagues reported a large Danish family with autosomal dominant FTD-3 (Gydesen et al. 1987; Brown 1998; Ashworth et al. 1999; Gydesen et al. 2002), and chromatin modifying protein 2B (*CHMP2B*) gene located on chromosome 3p11.2. FTD-3 is a rare form of FTD with only three *CHMP2B* confirmed pathogenic mutations (<http://www.molgen.ua.ac.be/FTDMutations>). The mode of inheritance is autosomal dominant. The age of symptomatic disease onset is from 46 to 65 years with mean of 57 years (Brown et al. 2004). Disease duration is from 5 to 21 years with mean of 10 years (Holm et al. 2007). In the early stage of disease, patients typically present with behavioral/personality changes and occasionally with dyscalculia. In the late stage of disease, particularly more than 4 years into the course of the illness, parkinsonian features such as rigidity, hypokinesia, reduced arm swing, and orofacial dyskinesia occur. The pyramidal signs can emerge in later stage of the illness in some patients (Gydesen et al. 2002; Ghanim et al. 2010). The presence of orofacial dyskinesias and parkinsonism could be at least partially related to neuroleptic medications required to control behavioral disturbances in these patients. However, they tend to be persisting and even progress after discontinuation of

neuroleptic medications indicating underlying dopaminergic deficits. Clinical features of FTD-3 are listed in Table 1.

ALS-FTD/*FUS*

FUS gene mutations were initially identified in familial and sporadic ALS cases in 2009 (Kwiatkowski et al. 2009; Vance et al. 2009). The *FUS* gene is located on chromosome 16p11.2. So far, only a single patient with FTDP phenotype (no ALS) has been reported (van Langenhove et al. 2010). This 52-year-old female exhibited aberrant behavioral and personality changes followed by rigidity 3 years later. No information was provided in regard to presence of other parkinsonian signs or therapy with levodopa. She was a carrier of M254V missense mutation located on exon 6 of *FUS* gene. Additional *FUS* gene R521C missense mutation carrier was identified with complex phenotype consistent of ALS, dementia, and parkinsonism (Yan et al. 2010). No details were provided about the specific features of parkinsonism in this case. Therefore, parkinsonism in carriers of *FUS* gene mutations is very rare and needs further delineation.

Familial FTDP with Known Linkage

At the present time, there is only one genetic locus located on chromosome 9 that is associated with FTDP phenotype.

FTDP with Linkage on Chromosome 9p

Vance et al. and Morita et al. independently described families originating from the Netherlands and Japan with chromosome 9p-linked FTD and ALS in 2006 (Morita et al. 2006; Vance et al. 2006). Later, additional kindreds with this linkage were reported in Europe (Le Ber et al. 2009; Pearson et al. 2011), North America (Momeni et al. 2006; Valdmanis et al. 2007; Boxer et al. 2011), and Australia (Luty et al. 2008). However, the pathogenic gene has not yet been identified. The mode of inheritance is autosomal dominant. A majority of cases exhibit the behavioral and personality changes as initial symptoms. Upper and lower motor neuron dysfunction usually occurs later in the course of the disease. About 26% of affected family members only have FTD signs, but 7% exhibit FTDP phenotype, occasionally accompanied with ALS. Parkinsonism is characterized by rigidity, bradykinesia, and tremor (from the description of cases, it is difficult to be certain about the type of tremor present). The symptomatic disease onset for FTDP cases with or without ALS phenotype is from 31 to 65 years with mean of 44 years. The disease duration is 3 to 12 years with mean of about 7 years. The response to levodopa is variable but can be present initially for both type of patients presented with either FTDP or FTDP with ALS phenotype. Additional details related to clinical features of FTDP with linkage on chromosome 9p are listed in Table 1.

Familial FTDP with Unknown Genetic Status

There are several disorders associated with the FTDP phenotype with unknown genes or linkage. In this review, we have chosen to discuss the familial progressive supranuclear palsy (PSP), hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS), and “overlap” syndrome. However, many other neurodegenerative disorders could be included in this category.

Familial PSP

Until very recently, PSP was considered to be a sporadic disorder (Davis et al. 1988). The community-based study from the Netherlands showed that up to 33% of cases are familial

and out of those 7% demonstrate autosomal-dominant inheritance (Donker Kaat et al. 2009). In this report, only a single case was found to be a carrier of *MAPT* P301L mutation. There are rare families with PSP/FTDP phenotype described in the literature dated back to before *MAPT* gene discovery in 1996 (examples include David et al. 1968; Mata et al. 1983; Ohara et al. 1992; Brown et al. 1993; de Yebenes et al. 1995; Tetrud et al. 1996; Gazeley and Maguire 1996) (David et al. 1968; Mata et al. 1983; Ohara et al. 1992; Brown et al. 1993; de Yebenes et al. 1995; Gazeley and Maguire 1996; Tetrud et al. 1996). Based on the literature available for our review, it is unknown if the affected family members from those kindreds were examined for the genetic status after the identification of the *MAPT* and *PGRN* genes. There are also rare families with PSP/FTDP phenotype that were described after the identification of the *MAPT* gene that have been tested for *MAPT* carrier status with negative results (example include families described in Donker Kaat et al. (2009) and unpublished Mayo Clinic Florida families). Review of Mayo Clinic Florida Brain Bank data of autopsy-proven PSP cases shows 12 families with negative molecular genetic testing for *MAPT* and *PGRN* gene mutations (unpublished data, courtesy of Drs. D. Dickson and R. Rademakers, an example of two such families is presented in Fig. 1). Therefore, it is reasonable to assume that more genes associated with PSP/FTDP phenotype and tau pathology will be found in the future. In the majority of these published and unpublished families, the mode of inheritance is autosomal dominant. The age of symptomatic disease onset is from 23 to 83 with mean of 64 years. The average disease duration is about 7.5 years. The ratio of male to female is 1 to 1.7. The clinical features of these cases usually resemble phenotype seen in sporadic PSP. However, behavioral impairments, personality abnormalities, and hallucinations are common in familial cases. Parkinsonism is usually symmetrical and is characterized by rigidity and bradykinesia with rest tremor seen infrequently. Levodopa therapy can be initially beneficial, but sustain response is rarely present. Additional clinical data are listed in Table 2.

HDLS

HDLS is a rare autosomal-dominant dysmyelination disease characterized by the presence of neuroaxonal swelling and spheroids (Wider et al. 2009). Eleven kindreds have been reported from seven countries including Sweden (Axelsson et al. 1984), Japan (Yazawa et al. 1997; Terada et al. 2004; Itoh et al. 2006) the Netherlands (van der Knaap et al. 2000), Australia (Hancock et al. 2003), USA (Marotti et al. 2004; Baba et al. 2006; van Gerpen et al. 2008), Germany (Mayer et al. 2007), and Portugal (Mendes et al. 2010). However, genetic cause remains unknown. The age of symptomatic onset is from 15 to 78 years with mean of 39 years. The mean disease duration is approximately 9 years. Psychiatric symptoms, behavioral and personality changes, parkinsonism, epilepsy, pyramidal signs, and ataxia are common clinical features. Parkinsonism is usually asymmetrical and is characterized by rigidity and bradykinesia and sometimes accompanied with tremor and/or dystonia. The response to levodopa is poor. Additional clinical features are listed in Table 2.

“Overlap” Syndrome

The term of “overlap” syndrome was coined by Uitti and colleagues in 1995 (Uitti et al. 1995). Patients with this condition exhibit signs of parkinsonism, MND, and dementia (Uitti et al. 1995). However, similar cases with complex phenotype were reported earlier as for example by Serle and Kovarik, Yvonneau et al., Alter and Schaumann, Gilbert et al., and Eisen et al. (Serle and Kovarik 1963; Yvonneau et al. 1971; Alter and Schaumann 1976; Gilbert et al. 1988; Eisen and Calne 1992). More recently, additional cases were studied by Mochizuki et al., Kuzuhara and Kokubo, Imamura et al., Portera-Cailliau et al., Schweitzer et al., McCluskey et al., and Gilbert et al. (Mochizuki et al. 2004; Kuzuhara and Kokubo 2005; Imamura et al. 2007; Portera-Cailliau et al. 2007; McCluskey et al. 2009; Schweitzer

et al. 2009; Gilbert et al. 2010). Positive family history for other neurodegenerative conditions is common. The genetic cause for many of these families has also not yet been discovered. The mean age of symptomatic onset is about 60 years. The mean disease duration is about 10 years. Male and female ratio is 2 to 1. Parkinsonism is characterized by asymmetrical bradykinesia and rigidity and is frequently an initial presentation. The rest tremor is also seen. In the early stage of disease, dementia and pyramidal signs occur followed by motor neuron disease (MND). However, the sequence of development of particular features could be reversed with MND or dementia associated with personality and behavior changes seen first and then followed by parkinsonism. There are also cases with phenotype that includes only two out of three cardinal features of this syndrome (Hirano et al. 1966; Qureshi et al. 1996; Desai and Swash 1999; Zoccolella et al. 2002; Konagaya et al. 2003; Morimoto et al. 2009). Levodopa therapy can be beneficial for majority of these patients. Clinical features of “overlap” syndrome are listed in Table 2.

Conclusion

Over the last two decades, tremendous progress has been achieved in better understanding of clinical and genetic aspect of familial forms of FTDP. Several genes, *MAPT*, *PGRN*, *CHMP2B*, and *FUS*, have been discovered allowing making a precise diagnosis in the clinical setting through genetic testing and counseling. However, there are still a number of families presenting with FTDP phenotype with unknown genetic cause. It remains to be seen if kindreds with FTD phenotype caused by the 43-kDa transactive response DNA binding protein (*TARDBP*) and *VCP* genes develop features of parkinsonism. In one family with *TARDBP* gene, vertical gaze palsy and choreiform movements of the upper extremities have been reported (Kovacs et al. 2009). Much needs to be learned about clinical–genetic correlations in these rare neurodegenerative disorders, albeit it is hoped that through studies of kindred curative treatments targeting specific genetic abnormalities in FTDP patients will be uncovered in the future.

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Fig. 1. Representative pedigrees of families with index cases autopsied demonstrating the presence of tauopathy and no *MAPT* gene mutations identified. *Squares* represent males, and *circles* represent females. *Arrow* indicates autopsy-proven PSP case. *Black symbols* indicate patients pathologically diagnosed with PSP. A *diagonal line* indicates a deceased person

Table 1

Clinical features of frontotemporal dementia associated with parkinsonism with known gene mutations/linkage

Name		FTDP-17T/ <i>MAPT</i>	FTDP-17U/ <i>PGRN</i>	FTD-3/ <i>CHMP2B</i>	FTD linked to 9p
Mode of inheritance		AD (for majority of cases nearly full penetrance, age dependent, no anticipation)			AD (reduced penetrance, age dependent, no anticipation)
Male:Female		1:1			
Mean AAO (range)		49 (25–76)	59 (48–83)	57 (46–65)	44 (31–65)
Mean DD (range)		7 (2–30)	7 (2–17)	10 (5–21)	7 (3–12)
Common clinical presentation	Early stage	B, Pe, Pa, L	B, Pe, C, L, Ps, Pa, CBS	B, Pe, C, L, Ps	B, Pe, C, MND
	Late stage	C, V, Py	D, Py	Pa ^b , Py ^b	Pa ^a , V
Rare clinical presentation		MND, E, Ps, L, CBS	MND, V, S	MND, E, V	Ps, O
Levodopa responsiveness		Can be temporarily effective usually early in disease course	Usually not beneficial with few exception (and if so also early in disease course)	Unknown	

FTDP-17T/MAPT frontotemporal dementia with parkinsonism linked to chromosome 17 with tau pathology due to *MAPT* gene mutations, *FTDP-17U/PGRN* frontotemporal dementia with parkinsonism linked to chromosome 17 with ubiquitin pathology due to *PGRN* gene mutations, *FTD-3/CHMP2B* frontotemporal dementia linked to chromosome 3 due to *CHMP2B* gene mutations, *MAPT* microtubule-associated protein tau, *PGRN* progranulin, *CHMP2B* chromatin modifying protein 2B, *AAO* age at onset, *DD* mean disease duration, *AD* autosomal dominant, *B* behavioral changes, *C* cognitive deficits, *D* dysphasia, *E* epilepsy, *L* language impairment, *O* oculomotor impairment, *Pa* Parkinsonism, *Pe* personality changes, *Py* pyramidal signs, *Ps* psychiatric symptoms, *S* semantic dementia, *V* visuospatial impairment, *CBS* corticobasal syndrome, *MND* motor neuron dysfunction (usually includes upper and lower motor neuron deficits)

^aThis feature also could be an initial presentation

^bThis feature can emerge in the late stage of disease, particularly more than 4 years into the course of the illness

Table 2

Clinical features of frontotemporal dementia associated with parkinsonism without known gene mutation/linkage

		Familial PSP	HDLS	“Overlap” syndrome
Mode of inheritance		AD (reduced penetrance, no anticipation)	AD	Unknown
Male:Female		1:1.7	1:1	2:1
Mean AAO (range)		64 (23–83)	39 (15–78)	60 (48–83)
Mean DD (range)		7.5 (1–16)	9 (2–17)	10 (0.4–26)
Clinical presentation	Early stage	Pa, B, Pe, O, Py, Dysp (in some cases)	Ps, B, Pe, Pa, Py, A, Co	Pa, MND, Ps
	Late stage	Co, Dyst	F, E ^a	Co ^a
Rare clinical presentation		Ps, E, A	V, S, Ch, Dyst, O	B, Pe
Levodopa responsiveness		Can be temporarily effective usually early in disease course	Poor	Can be effective

PSP progressive supranuclear palsy, *HDLS* hereditary diffuse leukoencephalopathy with axonal spheroids, *AAO* age at onset, *DD* disease duration, *FTDP* frontotemporal dementia with parkinsonism, *AD* autosomal dominant, *A* ataxia, *B* behavioral changes, *Ch* chorea, *Co* cognitive deficits, *Dysp* dysphasia, *Dyst* dystonia, *E* epilepsy, *F* focal cortical signs, *MND* motor neuron dysfunction, *O* oculomotor impairment, *Pa* Parkinsonism, *Pe* personality changes, *Py* pyramidal signs, *Ps* psychiatric symptoms, *S* sensory disturbance, *V* visuospatial impairment (usually includes upper and lower motor neuron deficits)

^aThis feature can emerge in the late stage of disease