Refining Frontotemporal Dementia With Parkinsonism Linked to Chromosome 17

Introducing FTDP-17 (MAPT) and FTDP-17 (PGRN)

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Frontotemporal dementia with parkinsonism (FTDP) is a major neurodegenerative syndrome, particularly for those with symptoms beginning before age 65 years. A spectrum of degenerative disorders can present as sporadic or familial FTDP. Mutations in the gene encoding the microtubule-associated protein tau (MAPT; OMIM *157140) on chromosome 17 have been found in many kindreds with familial FTDP. Several other kindreds with FTDP had been linked to chromosome 17, but they had ubiquitin-positive inclusions rather than tauopathy pathology and no mutations in MAPT. This conundrum was solved in 2006 with the identification of mutations in the gene encoding progranulin (PGRN; OMIM *138945), which is only 1.7 Mb centromeric to MAPT on chromosome 17. In this review, we compare and contrast the demographic, clinical, radiologic, neuropathologic, genetic, and pathophysiologic features in patients with FTDP linked to mutations in MAPT and PGRN, highlighting the many similarities but also a few important differences. Our findings describe an intriguing oddity of nature in which 2 genes can cause a similar phenotype through apparently different mechanisms yet reside so near to each other on the same chromosome.

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**Parkinsonism.**


Neurofilament inclusion body dementia, also known as neuronal

Multiple system atrophy; rarely associated with dementia

Dementia lacking distinctive histopathology

Frontotemporal lobar degeneration with ubiquitin-positive inclusions

Lewy body disease associated with mutations or duplications in the

Inclusion body myopathy with early-onset Paget disease and

Frontotemporal dementia and parkinsonism linked to chromosome 17

Frontotemporal lobar degeneration with motor neuron disease

Alzheimer disease

Frontotemporal dementia and parkinsonism linked to chromosome 17

Multisystem tauopathy

Argyrophilic grain disease

Progressive supranuclear palsy

Alzheimer disease

Pick disease

Corticobasal degeneration

Tauopathies (Tau)

Down syndrome

Familial British dementia with mutations in the gene encoding the
tableframe: Table 1. Specific Neurodegenerative Disorders Manifesting as Dementia With or Without Parkinsonism and Their Associated Dysfunctional Proteins

<table>
<thead>
<tr>
<th>Neurodegenerative Disorder (Dysfunctional Protein)</th>
<th>Amyloidopathies (Amyloid)</th>
<th>Tauopathies (Tau)</th>
<th>Synucleinopathies (α-Synuclein)</th>
<th>Tardopaties (TDP-43)</th>
<th>Unknown Dysfunctional Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>Alzheimer disease associated with mutations in the genes encoding amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2)</td>
<td>Pick disease</td>
<td>Alzheimer disease</td>
<td>Frontotemporal lobar degeneration with ubiquitin-positive inclusions</td>
<td>Dementia lacking distinctive histopathology</td>
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<td>Down syndrome</td>
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<td>Corticobasal degeneration</td>
<td>Alzheimer disease</td>
<td>Frontotemporal dementia and parkinsonism linked to chromosome 17</td>
<td>Frontotemporal lobar degeneration associated with mutations in the gene encoding microtubule associated protein tau (MAPT)</td>
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<tr>
<td>Familial Danish dementia</td>
<td>Familial Danish dementia with mutations in the gene encoding the integral membrane protein 2B (ITMP2B/BRI/FBD)</td>
<td>Argyrophilic grain disease</td>
<td>Frontotemporal dementia and parkinsonism linked to chromosome 17</td>
<td>Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia associated with mutations in the gene encoding α-synuclein (SNCA)</td>
<td>Frontotemporal dementia associated with mutations in the gene encoding chromatin-modifying protein 2B (CHMP2B)</td>
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<td>Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia associated with mutations in the gene encoding valosin-containing protein (VCP)</td>
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a Disorder that can manifest as frontotemporal dementia with or without parkinsonism.

typical age of onset varies between 25 and 65 years. Penetration appears to be close to 100%, though individuals living into old age without symptoms have been observed in families with at least 1 mutation (exon 10 + 16). The duration of symptoms from onset to death is typically 3 to 10 years. Symptomatology usually involves executive dysfunction and altered personality and behavior, with aphasia and parkinsonism evolving in many individuals. Memory impairment occurs less frequently as the primary presenting feature, and visuospatial impairment and limb apraxia are quite rare. Motor neuron
imaging are either absent or very mild.7 A similar topographic abnormality is typically seen on single-photon emission computed tomography and positron emission tomography scans, often with basal ganglia and/or thalamic hypoperfusion or hypometabolism. Pathologically, cortical atrophy is as indicated on imaging studies, sometimes accompanied by argyrophilic grain disease, or Pick disease if the presence of an MAPT mutation was not known.

3 With closer inspection, how similar are the clinical phenotypes associated with mutations in MAPT and PGRN? While our knowledge of the full spectrum of clinical, radiologic, and pathologic issues in FTDP associated with mutations in PGRN is still evolving, interesting findings have already emerged that allow comparisons
between MAPT’s and PGRN’s mutation-associated characteristics (based on published findings to date and unpublished data from our group) (Table 3). The frequency of mutations in PGRN in FTD series is similar to that in MAPT. With at least 35 mutations identified to date, almost as many mutations in PGRN have been discovered in less than 1 year than in the 8 years since the initial identification of mutations in MAPT. The mode of inheritance follows an autosomal dominant pattern but with reduced penetrance (only 90% of carriers develop symptoms by age 70 years). There are multiple known PGRN mutation carriers who are asymptomatic in their 70s, and at least 1 known affected individual developed symptoms after age 80 years. The clinical features and particularly the syndromic diagnoses have been more variable than in MAPT mutation carriers, with not only behavioral and cognitive features commonly present, but also memory impairment, limb apraxia, parkinsonism, and visuospatial dysfunction, leading to cases being diagnosed with mild cognitive impairment, Alzheimer disease, Parkinson disease, Parkinson disease with dementia, and dementia with Lewy bodies in addition to FTD with or without parkinsonism and 1 of the progressive aphasia syndromes. The diagnosis of corticobasal syndrome has also been particularly frequent in the cases reported thus far, while no patient with a definite pathogenic PGRN mutation has been reported to date with an ALS phenotype.

As one would expect, based on the clinical features of apraxia and visuospatial dysfunction, greater parietal involvement is clearly present in many PGRN mutation cases, which is also reflected on imaging and pathologic studies. In some cases, rather striking signal changes on magnetic resonance imaging are present, which is rarely seen in MAPT mutation carriers. Another curious observation is the tendency in some kindreds for the same cerebral hemisphere to be maximally involved in most or all affected members of a family, such as a progressive aphasia syndrome with maximal left hemisphere involvement and the corticobasal syndrome with or without FTD features with maximal right hemisphere involvement, to our knowledge, this tendency has not been noted among any kindreds with MAPT mutations.

On histologic examination, the consistent finding is FTLD with ubiquitin-positive inclusions with neuronal intranuclear inclusions. Immunostaining directed against progranulin stain normal structures within neurons and activated microglia. However, the ubiquitinated inclusions are not progranulin immunoreactive; rather, transactive response DNA–binding protein 43 was very recently discovered to be a major ubiquitinated protein in both neuronal cytoplasmic and intranuclear inclusions in PGRN mutation cases. Moreover, transactive response DNA–binding protein 43 is also present in neuronal ubiquitin-positive inclusions in FTD with ubiquitin-positive inclusions, FTLD with motor neuron disease, and idiopathic ALS.

Also contrasting with MAPT is the mechanism of disease with PGRN mutations—all PGRN mutations identified thus far create functional null alleles that cause a partial reduction in progranulin production or haploinsufficiency. This disease mechanism may allow a more straightforward approach for treatment by either replacing progranulin or using drugs to increase production or secretion of progranulin from the remaining normal PGRN allele.

The net effect of 2 genes linked not only by proximity but also by most overlapping and expanding features requires refinements in our conceptual framework and nomenclature in FTDP. An obvious solution to this problem is to simply refine the term by including reference to the genetic cause of the disease in each case, and thus FTDP-17 could be subdivided into FTDP-17 (MAPT) and FTDP-17 (PGRN). This approach has the advantage of employing a now widely used, if not always completely appropriate, clinical terminology, refining it to reflect that ultimately these conditions are defined by their genetics rather than their clinical or pathological phenotypes. The scientific community has clearly just begun to expand the characterization and refine the nomenclature of familial disorders linked to chromosome 17.

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**REFERENCES**


