Supplementary Data

C9ORF72 Repeat Expansions in the Frontotemporal Dementias Spectrum of Diseases: A Flow-chart for Genetic Testing

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Patients with isolated parkinsonism at onset

Patient 1. The proband developed a parkinsonian syndrome at age 55. Initially, he had gait disorders with instability and falls, mainly caused by a severe leg tremor at rest and when walking. At age 57, he needed a cane, then a walker. He developed a restless legs syndrome and sleep disorders characterized by nocturnal agitation during REM sleep. On examination, axial rigidity and akinesia with camptocormia, and left-predominant limb rigidity and akinesia were present. Oculomotricity was normal. Limb reflexes were enhanced. His symptoms and gait partially improved with ropinirole. The UPDRS was 27. A DaTScan showed bilateral presynaptic dopaminergic denervation of the striatum. At age 58, he developed progressive distal motor weakness in the lower limbs and left upper limb, associated with distal amyotrophy, fasciculations, bilateral plantar extensor, and a dropped head. There were no bulbar symptoms. Motor neuron disease was confirmed by electromyogram. He developed aggressiveness, irritability, impulsiveness, and indifference to others. His Mini-Mental State Exam (MMSE) score was 25/30. Brain magnetic resonance imaging (MRI) revealed moderate cortical atrophy. His mother had dementia at age 55 and died at age 72. He developed aggressiveness, irritability, impulsiveness, and indifference to others. His Mini-Mental State Exam (MMSE) score was 25/30. Brain magnetic resonance imaging (MRI) revealed moderate cortical atrophy. His mother had dementia at age 55 and died at age 72. His sister presented severe and recurrent depression at age 55, and was followed by a psychiatrist.

Patient 2. The patient presented with a parkinsonian syndrome at age 48, beginning with a bilateral lower limb tremor at rest and akinesia. She received levodopa (375 mg per day) and ropinirole with little effect. The symptoms progressively worsened. At age 54, she had bilateral upper limb rest tremor, bradykinesia, axial rigidity, and a severe gait disorder due to lower limb akinesia and freezing. She was dysarthric, hypophonic, with urinary incontinence. Ophthalmoplegia, hallucinations, pyramidal symptoms, apraxia, and dementia were absent. The MMSE score was 29/30. Her husband described sleep disorders and somnambulism.
A DaTScan showed predominantly right presynaptic dopaminergic denervation of the striatum. She developed mild cognitive disorders at age 56; 9 years after disease onset. Her MMSE score was 25/30 (-2 in calculation, -1 repetition, -2 recall). At age 57, her Unified Parkinson’s Disease Rating Scale (UPDRS) was scored 7 on, 20 off and her Hoehn and Yahr score was 4. She died at age 59.

Patients with isolated primary lateral sclerosis at onset

**Patient 1.** The patient had isolated upper motor neuron disease revealed by a spastic paraparesis at age 30. She had a spastic gait with muscular weakness in the lower limbs and required a walker. On examination, reflexes were enhanced in the four limbs, and bilateral extensor plantar reflexes were observed. She had no bulbar symptoms. The upper motor symptoms progressed slowly and remained isolated for 22 years. Primary lateral sclerosis (PLS) was diagnosed. At age 52, she developed apathy, was socially withdrawn and performed rituals. Two years later, the MMSE score was 29/30 and the frontal assessment battery score was 14/18. On examination, reflexes of the four limbs were enhanced with lower limb spasticity and distal muscular weakness. Amyotrophy, fasciculations, and bulbar symptoms were absent. She is alive at age 56. Her sister had behavioral variant frontotemporal dementia (bvFTD) at age 48, but no motor neuron disorder. Her mother had FTD-ALS and died at age 62.

**Patient 2.** The proband showed personality changes and had behavioral disorders at age 45. He was aggressive, irritable, expressed anger, and spent money excessively. At age 48, he was disinhibited and presented hyperorality, impulsiveness, joviality, emotional lability, and imitation behavior. Reflexes were enhanced and bilateral plantar extensor reflexes were observed. He had spasticity but no muscular weakness or fasciculations. His speech was dysarthric and agrammatical, with stuttering. The neuropsychological evaluation showed dysexecutive alterations. The MMSE score was 22/30. The isolated upper motor neuron signs that progressed slowly over a long period were consistent with primitive lateral sclerosis associated with bvFTD. The patient was institutionalized at age 54. He presented moderate akinesia and rigidity. At age 56 he was mute and severely apathetic. His tongue was amyotrophic, but no fasciculations were noted. He developed amyotrophy in the left hand and fasciculations in the upper limb. He died at age 56.
### Supplementary Figure 1
Relative frequencies of mutations in C9ORF72, PGRN, MAPT, VCP, TARDBP, and FUS/TLS genes in patients with (A) familial FTD and (B) familial FTD-ALS.

<table>
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<th>Gene</th>
<th>Frequency</th>
</tr>
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<tr>
<td>C9ORF72</td>
<td>12.8%</td>
</tr>
<tr>
<td>PGRN</td>
<td>13.7%</td>
</tr>
<tr>
<td>TARDBP</td>
<td>0.4%</td>
</tr>
<tr>
<td>FUS/TLS</td>
<td>0%</td>
</tr>
<tr>
<td>MAPT</td>
<td>10.3%</td>
</tr>
<tr>
<td>VCP</td>
<td>4.3%</td>
</tr>
<tr>
<td>Unknown</td>
<td>58.5%</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9ORF72</td>
<td>65.9%</td>
</tr>
<tr>
<td>PGRN</td>
<td>0%</td>
</tr>
<tr>
<td>TARDBP</td>
<td>2.2%</td>
</tr>
<tr>
<td>FUS/TLS</td>
<td>0.7%</td>
</tr>
<tr>
<td>MAPT</td>
<td>0%</td>
</tr>
<tr>
<td>VCP</td>
<td>0%</td>
</tr>
<tr>
<td>Unknown</td>
<td>31.2%</td>
</tr>
</tbody>
</table>

### Supplementary Figure 2
Clinical presentation at disease onset and diagnosis at inclusion after a disease progression of 3.7 years. AD: Alzheimer’s disease; ALS, amyotrophic lateral sclerosis; aMCI, amnestic mild cognitive impairment; bvFTD, behavioral frontotemporal dementia; CBDS, corticobasal degeneration syndrome; PLS, primary lateral sclerosis; PSP, progressive supranuclear palsy; PNFA, progressive non-fluent aphasia; SD, semantic dementia. The number of probands and relatives with each phenotype is indicated in brackets (probands/relatives).

- 4 PNFA
- 2 semantic dementia
- 8 psychosis
- 2 aMCI
- 137 bvFTD
- 1 CBS
- 21 bvFTD-ALS
- 1 bv-FTD-ALS
- 1 LS
- 24 ALS
- 1 92 bvFTD
- 55 FTD-ALS
- 1 FTD-ALS
- 1 FTD-PLS
- 1 LS-FTD
- 9 ALS-FTD
- 15 ALS
- 1 PSN
- 1 PSP

Diagnosis at inclusion (after a disease progression of 3.7 years): 4 PNFA

92 bvFTD

55 FTD-ALS

B8 FTD-ALS/PLS

9 ALS-FTD

15 ALS

1 PSN

1 PSP
Supplementary Figure 3. Cox regression curves showing the cumulative probability of onset (A) and the cumulative probability of survival from disease onset (B) according to the mutation: C90RF72, PGRN, MAPT, and FTD patients with no identified mutations (other). Onset in C90RF72 patients occurred later than in MAPT patients (46.8, 95%CI: 43.0–50.6) and earlier than in FTD patients without mutations (61.2, 95%CI: 59.8–62.7), but did not significantly differ from onset in PGRN patients (59.63 years; 95%CI: 57.6–61.5). The mean disease duration at death was significantly shorter in C90RF72 patients (9.5 years, 95%CI: 8.0–11.0) than in FTD patients with no mutations (other, 10.5, 95%CI: 9.5–11.6); it did not differ significantly from disease durations in PGRN (8.3, 95%CI:6.8–9.8, p = 0.99) and MAPT patients (10.5 years; 95%CI 8.2–12.8; p = 0.17).