

# Dementia in SPG4 hereditary spastic paraplegia

## Clinical, genetic, and neuropathologic evidence



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### ABSTRACT

**Background:** Cognitive impairment and dementia has been reported in autosomal dominant hereditary spastic paraparesis (HSP) linked to the SPG4 locus. There has only been one postmortem examination described; not all accept that progressive cognitive decline is a feature of this disorder.

**Objective:** A family with SPG4-HSP known to have a deletion of exon 17 in the spastin gene (SPG4delEx17) was cognitively assessed over a 7-year period. The index family member died and a postmortem examination was performed.

**Methods:** Thirteen family members older than 40 years were clinically and cognitively assessed using the Cambridge Cognitive Assessment over a 7-year period. The presence of SPG4delEx17 was assessed; a neuropathologic examination of the brain of the index family member was performed.

**Results:** Cognitive decline occurred in 6 of the 13 family members and in all 4 older than 60 years. Two genetic deletions were identified: SPG4delEx17 in 12 of the 13 family members and a deletion of SPG6 (SPG6del) in 5. Eight individuals had the SPG4delEx17 deletion only; 4 had evidence of progressive cognitive impairment. Four family members had both SPG4delEx17 and SPG6del; 2 of these had cognitive impairment. One family member with the SPG6del alone had neither HSP nor cognitive impairment. The index case with both deletions died with dementia; the brain showed widespread ubiquitin positivity within the neocortex and white matter.

**Conclusion:** Cognitive decline and dementia is a feature of SPG4-HSP due to a deletion of exon 17 of the spastin gene. *Neurology*® 2009;73:378–384

### GLOSSARY

**ALS** = amyotrophic lateral sclerosis; **CAMCOG** = Cambridge Cognitive Examination; **CAMDEX** = Cambridge Mental Disorders of Elderly Examination; **FTD** = frontotemporal dementia; **HSP** = hereditary spastic paraparesis; **MLPA** = multiplex ligation-dependent probe amplification; **MMSE** = Mini-Mental State Examination.

Hereditary spastic paraparesis (HSP) encompasses a heterogeneous group of inherited neurodegenerative disorders with the main clinical feature of slowly progressive spasticity and weakness of the legs.<sup>1</sup> Patients with additional abnormalities are considered to have complicated HSP while those without are classified as having pure HSP.<sup>2</sup> The most common type of HSP is autosomal dominant HSP, of which 45% is due to mutations or deletions in the *SPAST* gene on chromosome 2p (SPG4 locus).<sup>3</sup> Although considered a pure form of HSP, some families with SPG4-linked HSP have been reported to have cognitive impairment.<sup>4–12</sup> Some have suggested that the cognitive impairment, when it occurs, is mild and subclinical<sup>13,14</sup>; not all accept the hypothesis that progressive cognitive impairment is an intrinsic feature of SPG-4 linked HSP<sup>9</sup> and further work has been suggested.<sup>15</sup> A neuropathologic study of a patient who developed a late-onset dementing illness, from a family with SPG4-linked HSP due to a missense mutation in exon 10 of the spastin gene, is of relevance.<sup>9</sup> In this article, we describe the neuropathologic features of the dementia of the index case of a large family with SPG4-linked HSP,<sup>4</sup> recently found to have a deletion of exon 17 of the *SPG4* gene<sup>16</sup> and some family

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**Table 1** The 13 members of the family with SPG4-linked hereditary spastic paraparesis (HSP), who were older than 40 years of age in 2007, in relation to the age at onset of their symptoms of HSP, the presence or absence of deletions in exon 17 of the *SPG4* gene (SPG4del17), and the microdeletion of the *SPG6* gene (SPG6del), their cognitive assessments in 2000 and 2007, and their clinical disability in 2007

Patient/ gender	Age at onset of HSP, y	Age in 2007, y	SPG4delEx17	SPG6del	CAMCOG examination		
					2000	2007	HSP disability 2007
III-4/F (Index)	38	Died 2003 age 73	Y	Y	69	47 (2002)	Dead
III-6/M	39	77	Y	Y	75	Dementia	Wheelchair
III-7/M	68	76	Y	N	68	50	Minimal disability
III-12/M	63	66	Y	N	81	75	Minimal disability
III-13/M	N/A	64	Y	N	91	73	No signs/symptoms
IV-13/M	26	54	Y	N	99	101	Two sticks
IV-15/M	34	49	Y	N	104	101	One stick
IV-16/F	46	46	Y	Y	94	91	Minimal disability
IV-17/F	N/A	42	Y	Y	98	87	Affected asymptomatic
IV-18/F	38	40	Y	N	100	95	Minimal disability
IV-19/F	35	48	Y	N	72	71	Minimal disability
IV-20/M	N/A	40	Y	N	88	78	No signs/symptoms
IV-28/M	N/A	57	N	Y	NE	95	No signs/symptoms

CAMCOG = Cambridge Cognitive Examination; N/A = not applicable; NE = not examined.

members were also found to have a deletion in the *NIPA1* gene (*SPG6* locus). We also present longitudinal cognitive assessments in the older patients from the same family in order to characterize the dementia in relation to the deletions in *SPG4* and *SPG6* genes.

**METHODS Subjects.** This family had been identified during an epidemiologic study of HSP in Ireland approximately 12 years ago and had been followed at regular intervals.<sup>4</sup> For the purposes of this study only family members older than 40 years in 2007 were assessed clinically, cognitively, and genetically. All consenting members gave a detailed neurologic history, gave a blood sample for DNA extraction, and were examined by one of 3 neurologists (asymptomatic family members were examined by 2 neurologists). This study was approved by St. Vincent's University Hospital Ethics Committee.

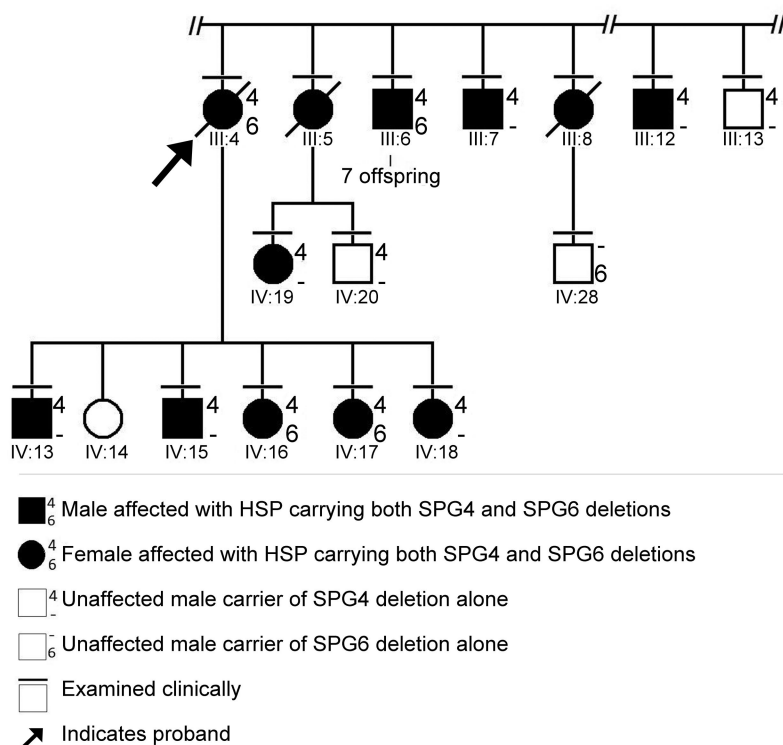
**Clinical and cognitive assessment.** Family members were considered definitely affected with HSP if they had a progressive gait disturbance and frank signs of a corticospinal tract deficit in the lower limbs with hyperreflexia and extensor plantar responses.<sup>17</sup> Subjects were considered probably affected if they were asymptomatic but had lower limb hyperreflexia and extensor plantar responses. Three of the older family members had been extensively investigated, including brain MRI, for other causes of cognitive decline. All members older than 40 years of age and who had a previous cognitive examination in 2000 were assessed using the Cambridge Cognitive Examination (CAMCOG), the cognitive portion of the Cambridge Mental Disorders of Elderly Examination (CAMDEX).<sup>18</sup> The CAMCOG incorporates items from the Mini-Mental State Examination (MMSE) with further items covering additional aspects of cognitive function including calculation, perception, abstraction, attention, praxis, memory, language, and orientation. The maximum total CAMCOG score is 105. A score of 60–80 indicates mild cognitive impairment,

35–59 moderate dementia, and <35 severe dementia, while a score >80 is considered normal.

**Method of genetic assessment.** Blood was taken from all consenting individuals. DNA was extracted from whole blood using QIAamp® DNA Blood Mini kit (Qiagen). DNA was eluted from QIAamp Mini spin columns with 50 µL of elution buffer. Multiplex ligation-dependent probe amplification (MLPA) reactions and quantitative analysis of raw MLPA data were performed as described previously.<sup>19</sup> The initial investigation on the index patient utilized MLPA probe set P165 (MRC-Holland, The Netherlands), which targets all exons of *SPAST* and of *SPG3A*. We subsequently aimed to determine the 3' extent of the *SPAST* deletion identified and therefore applied P211. This probe set analyzes the genomic region flanking *SPAST* on chromosome 2 but also contains probes directed against *NIPA1* and neighboring genes on chromosome 15. P211 was further used to reveal the deletion status of both *SPAST* and *NIPA1* in the rest of the pedigree.

**RESULTS Genetic.** A deletion of exon 17 of the *SPAST* gene, SPG4delEx17, was identified by MPLA in 12 of the 13 family members older than 40 years (table 1, figure 1).<sup>16</sup> In addition, a second microdeletion <300 kb on chromosome 15q, SPG6del, was also identified in 5 of the 13 family members. This region comprises 4 highly conserved genes located between BP1 and BP2, a region that is commonly deleted in Prader-Willi syndrome, including *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5*. Four of the 5 family members with the SPG6 deletion (III-4, III-6, IV-16, IV-17) also had the SPG4delEx17 deletion (table 1, figure 1). Only one individual (IV-28) had the SPG6 deletion without SPG4delEx17; he was 57 years old in 2007 and was

**Figure 1** Family tree of the SPG4-linked hereditary spastic paraparesis (HSP) pedigree



Part of the family tree of the SPG4-linked HSP pedigree illustrating the relationships between the family members, the presence of HSP (filled symbols), and the presence or absence of deletions in exon 17 of the SPG4 gene (indicated by 4) and the microdeletion of the SPG6 gene (indicated by 6). The proband is III-4. The diagonal slash through a symbol indicates deceased.

clinically normal without cognitive impairment (table 1, figure 1).

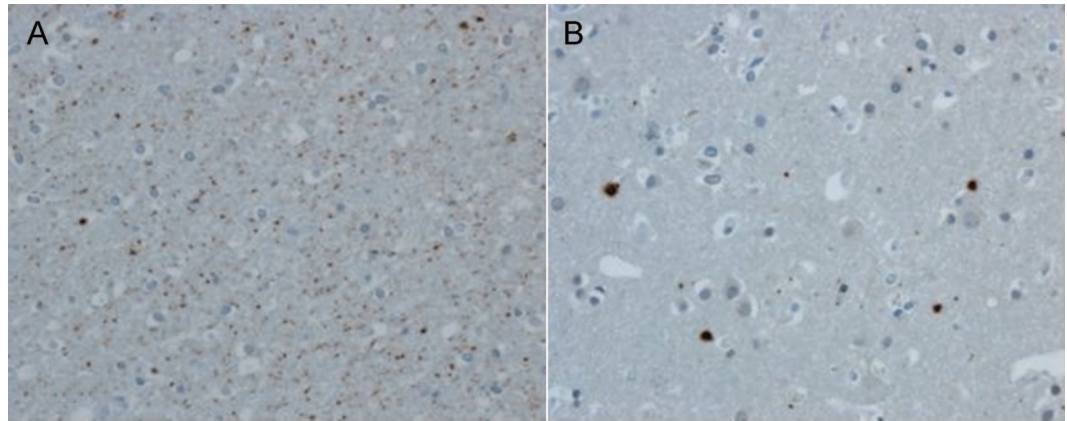
**Clinical and cognitive assessment in relation to genetic results.** Details of the clinical assessments in 2007 and CAMCOG results in 2000 and 2007 are given in table 1. Of the 12 family members with SPG4delEx17, 9 were affected and symptomatic (one of whom had died in 2003), one was affected but asymptomatic (IV-17), and 2 were clinically unaffected carriers (III-13, IV-20); the older nonpenetrant individual (III-13) was 64 years old in 2007. The range of age at HSP symptom onset was 26–68 years. Of the 9 affected symptomatic family members at follow-up, 6 walked independently, 1 used one stick, 1 used 2 crutches, and 1 was wheelchair bound. All 5 individuals older than 60 years with SPG4delEx17 had evidence of cognitive decline over the previous 7 years; the index case (III-4) had a CAMCOG score of 69 at the age of 70 years in 2000 and subsequently deteriorated with a severe dementia (see case report); she carried both deletions of SPG4 and SPG6. Her brother (III-6), now wheelchair bound, also carries both deletions, had cognitive impairment in 2000, and by report from his physician

had further cognitive deterioration with frank dementia in 2007; a CAMCOG examination was not performed in 2007. Three other family members older than 60 years (III-7, III-12, III-13), who carry only SPG4delEx17, showed evidence of cognitive decline between 2000 and 2007; 1 of these 3 at the age of 64 years (III-13) was clinically unaffected by HSP. Cognitive impairment (CAMCOG <80) was also noted in two other family members with only the SPG4delEx17 deletion (IV-19, IV-20) aged 48 and 40 years at assessment in 2007. In one of these (IV-19), there had been no deterioration in the CAMCOG score over the preceding 7 years and this may represent a constitutional cognitive impairment; in the other family member (IV-20), aged 40 in 2007, the CAMCOG score in the period 2000 to 2007 had fallen by 10 points into the mildly cognitively impaired range (CAMCOG score 78). The single family member with the SPG6del alone (IV-28) had no signs of HSP and a normal CAMCOG score of 95 at the age of 57 years. Three other family members, not listed in table 1, affected by HSP died during the period 2000–2004; none were genotyped. All were over age 60 with evidence of cognitive impairment on CAMCOG (range of scores 60–75) in 2000; postmortem was not obtained in these 3 family members. In 3 of the older members of the family, III-4, III-6, and III-7, other investigations for dementia, including brain MRI, were negative.

**Index case (III-4).** This woman had a progressive spastic paraparesis from the age of 38 years; in 1995, at the age of 65, she was wheelchair bound and was admitted to the hospital for treatment of a urinary tract infection. On a Short Test of Mental Status, she scored of 23 out of 38 (normal >28). Neuropsychological testing revealed impairments in performance IQ on the Wechsler Adult Intelligence Scale–Revised, verbal and nonverbal memory, information processing speed, verbal fluency, and perceptual judgment.<sup>4</sup> In August 2001, she was admitted to long-term care; family members reported increasing confusion, she did not recall visitors or recognize family members, she became disorientated in time and place, and eventually she became completely bedbound. Repeated cognitive assessment showed CAMCOG scores falling from 69 (mild dementia) in 2000 to 47 (moderate dementia) in 2002, a fall of 21 points in just over 18 months. Behavioral assessment with the Neuropsychiatric Inventory at this time gave a total score of 20/120 with reports of minimal agitation and tearfulness, moderate apathy, and mood lability, but no other significant endorsements.<sup>20</sup> She died in 2003 at the age of 73 due to



**Figure 2** Ubiquitin immunostained postmortem hereditary spastic paraparesis brain: White matter and cortex



(A) Ubiquitin immunostained representative section of white matter showing extensive dot positivity in the neuropil. Magnification  $\times 20$ . (B) Ubiquitin immunostained representative section of cortex showing dot positivity in the neuropil. Magnification  $\times 40$ .

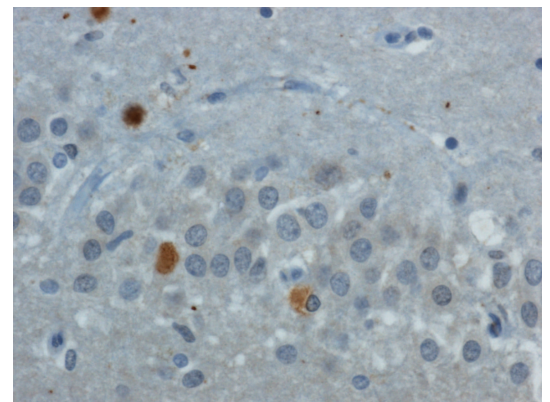
bronchopneumonia; permission for a postmortem examination was given.

**Neuropathology of III-4.** The formalin-fixed brain (1,275 g) showed very mild hydrocephalus ex vacuo. The spinal cord was markedly atrophic particularly in the thoracic and lumbar regions. Standard brain blocks were stained with hematoxylin and eosin, and were immunoreacted with antibodies to  $\beta$ -A4 (Dako), phosphorylated tau (BioSource), neurofilament (Synbio),  $\alpha$ -synuclein (Chemicon), glial fibrillary acidic protein (Dako), ubiquitin (Dako), and TDP-43 (Proteintec). Microscopic examination showed minimal linear frontotemporal superficial spongiosis. The hippocampus putamen, globus pallidus, internal capsule, entire brainstem, and cerebellum appeared normal. The substantia nigra showed mild pigmentary incontinence but Lewy bodies were not present. The most notable feature was widespread ubiquitin positivity in the form of dots and grains within all areas of neocortex and white matter (figure 2, A and B). Rare isolated ubiquitin-positive intraneuronal cytoplasmic inclusions were present in the dentate fascia (figure 3). Rare isolated tau-positive tangles were present in the frontal and temporal neocortex and in the hippocampus. Immunostaining for  $\beta$ -amyloid,  $\alpha$ -synuclein, and TDP-43 was negative in all areas. The spinal cord demonstrated bilateral symmetric tract degeneration involving the dorsolateral and ventral corticospinal tracts. Anterior horn cell loss was not present. In the only previously reported case of HSP-related dementia, there were a variety of additional changes not present in this case (table 2).<sup>9</sup>

**DISCUSSION** In this longitudinal clinical, genetic, and neuropathologic study, we have documented that progressive cognitive decline occurs in this fam-

ily with SPG4-linked HSP. Two genetic deletions were identified: SPG4delEx17 and SPG6del. Four family members had both SPG4delEx17 and SPG6del; the index case with both deletions died with dementia; the neuropathologic findings differed from the only previously reported case of dementia in SPG4-linked HSP.<sup>9</sup> Eight individuals had the SPG4delEx17 deletion only; 6 were definitely affected, 2 were clinically unaffected carriers. Four of these family members (III-7, III-12, III-13, IV-20) with only the SPG4delEx17 had evidence of progressive cognitive impairment. The single individual with the SPG6del alone was clinically unaffected, without evidence of cognitive impairment at the age of 57 years.

**Figure 3** Ubiquitin immunostained postmortem hereditary spastic paraparesis brain: Dentate fascia



Ubiquitin immunostained section of dentate fascia showing cytoplasmic positivity in dentate neurons. Magnification  $\times 60$ .

**Table 2** Comparison of the neuropathologic findings between the case of dementia in association with SPG4-linked autosomal dominant hereditary spastic paraparesis (ADHSP) reported by White and colleagues<sup>9</sup> and the findings in our index case (III-4) with deletions in exon 17 of the *SPG4* gene and a microdeletion of the *SPG6* gene

Neuropathology	ADHSP and dementia, spastin A1395G missense mutation (White et al., 2000 <sup>9</sup> )	ADHSP and dementia, deletions of exon 17 of <i>SPG4</i> and <i>SPG6</i> , Index case III-4
a-Synuclein LBs—substantia nigra	Present	Absent
CA1 depletion	Present	Absent
Tangles in surviving neurons	Present	Present—rare
Ballooned neurons	Present	Absent
Tau-positive oligo inclusions	Present	Absent
Tau-positive astrocytic inclusions	Present	Absent
Ubiquitin-positive intraneuronal inclusions	Absent	Rare
Ubiquitin-positive dots; grains; dystrophic neurites	No comment	Widespread

LBs = Lewy bodies.

The clinical phenotype of HSP in this family is similar to that reported in SPG4-linked HSP: variably late age at onset, slow progression, incomplete penetrance, and intrafamily variability.<sup>21</sup> About 20% of carriers of SPG4-HSP are asymptomatic and 6% are unaffected carriers.<sup>3</sup> Deletions as a cause of SPG4-HSP are found in up to 20% of all SPG4 HSP cases.<sup>16</sup>

The second genetic deletion identified in this family was SPG6del on chromosome 15q. This region between BP1 and BP2 can be deleted in Prader-Willi syndrome as part of a larger deletion that extends to BP3. While the region between BP2 and BP3 contains imprinted genes, the region between BP1 and BP2 contains 4 highly conserved nonimprinted genes: *NIPAI*, *NIPA2*, *CYFIP1*, and *TUBGCP5*. Missense mutations of *NIPAI* have been described as causing the clinical phenotype of autosomal dominant HSP.<sup>22</sup> *NIPAI* has recently been shown to encode a functional membrane magnesium transporter.<sup>23</sup> It is suggested that the *NIPAI* mutation T45R acts through a dominant negative gain of function since haplotype insufficiency for *NIPAI*, often seen in patients with Prader-Willi or Angelman syndrome, does not result in the HSP phenotype in these patients.<sup>24</sup> Prader-Willi patients with haploinsufficiency for *NIPAI*, *NIPA2*, *CYFIP1*, and *TUBGCP5* (BP1 to BP3 deletion) are reported to have more behavioral and psychological problems than patients with the smaller BP2 to BP3 deletion. A single case report of BP1 to BP2 deletion was described in a child with severe speech impairment and mental retardation and his father who had a milder phenotype with slow understanding and low intelligence.<sup>25</sup> In our family, only one individual had this deletion without the SPG4delEx17, and is clinically unaf-

fected at 57 years of age with a normal CAMCOG score. Four family members carry SPG6del in addition to SPG4delEx17: 1 died with a severe dementia (case III-4), 1 has dementia and is disabled with HSP (III-6), 1 aged 46 has HSP (IV-16), and 1 aged 42 has HSP but is asymptomatic (IV-17); both IV-16 and IV-17 have normal CAMCOG scores. Thus this deletion, SPG6del, appears not to have a clinical phenotype in this family. Seven of the 12 individuals with SPG4delEx17, and of those all 4 individuals older than 60 years, had CAMCOG scores in the cognitively impaired range. In addition, 3 other family members with HSP, but not genotyped, died with associated cognitive impairment in the period 2000–2004. In most cases the dementia developed years after the onset of HSP but in one family member (III-13) with SPG4delEx17, cognitive deterioration has occurred without any signs of HSP. This is in keeping with previous studies of cognitive impairment in SPG4-linked HSP.<sup>6,8,13</sup> However, in contrast to some suggestions,<sup>15</sup> the dementia does not necessarily parallel the severity of the HSP but appears to relate to age.

Neuropathologic examination of the index case revealed subtle alterations in brain structure dominated by superficial spongiosis and widespread ubiquitin immunopositivity. There was an absence of amyloid-related pathology and the density of tau-positive tangles was no more than might have been expected from age-related change alone. This ubiquitin-related neuropathology is not of itself unique, and may be seen in normal aging. However, the combination of widespread ubiquitin immunopositivity and superficial spongiosis is similar to that seen in previously reported amyotrophic lateral sclerosis (ALS)–dementia cases.<sup>26</sup> Additionally, the neuropathology differs remarkably from that observed in the only other reported case of SPG4-linked HSP with dementia (table 2). However, the clinical phenotype, time course of the illness, and presence of genetic abnormalities exclude motor neuron disease in this patient. Furthermore, the autopsy did not demonstrate any evidence of anterior horn cell loss or evidence of bulbar involvement. Nevertheless, the neuropathologic findings in our case most closely resemble those described in sporadic, non-Guamian ALS, where the density and extent of ubiquitin-positive,  $\alpha$ -synuclein and tau-negative neuronal inclusions and dystrophic neurites in cognitively impaired individuals with ALS greatly exceeds that of cognitively normal individuals with ALS.<sup>26,27</sup> The case reported here also demonstrates superficial linear spongiosis, a feature which reliably distinguishes cognitively impaired and cognitively intact ALS groups.<sup>26</sup>

The dementia associated with this pedigree has been reported previously with detailed descriptions of the neuropsychological and behavioral profile.<sup>4,6,8</sup> In line with the pathologic resemblance to ALS, our pedigree shares some similarities with the dementia of ALS, which is regarded as overlapping clinically and pathologically with frontotemporal dementia (FTD).<sup>28</sup> ALS dementia presents with executive and memory deficits but most characteristically with language dysfunction in the form of progressive nonfluent aphasia and/or profound behaviour change consistent with the behavioral variant of FTD. Our family shows executive dysfunction, memory, and language deficits combined with a degree of behavioral change and so shares some similarities with ALS/FTD. However, we did not see the progressive aphasia or typical, florid disinhibition, stereotypy, apathy, and psychosis one sees with ALS/FTD, so one could not regard them as identical.

These findings lend support to the hypothesis that cognitive loss and dementia is intrinsic to the natural history of some families with SPG4-linked autosomal dominant HSP. Progressive cognitive impairment develops from the age of 60 years or earlier.<sup>6</sup> One unaffected carrier, without clinical evidence of spastic paraparesis (III-13), also demonstrated a decline in CAMCOG scores into the cognitively impaired range over time. The neuropathologic examination showed evidence of a structural correlate of the dementia in SPG4-linked HSP. We acknowledge that the presence of the SPG6 microdeletion is potentially confounding and given the degree of clinical variation in this and other forms of HSP, it is impossible to rule out a role for this deletion. Further studies from other neurologists with well-defined HSP families are needed; perhaps in such a relatively rare disorder, a prospective multicenter study following SPG4-linked HSP families using uniform assessment instruments is the way forward.

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## DISCLOSURE

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