**SPG10 is a rare cause of spastic paraplegia in European families**

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**ABSTRACT**

**Background:** SPG10 is an autosomal dominant form of hereditary spastic paraplegia (HSP), which is caused by mutations in the neural kinesin heavy chain KIF5A gene, the neuronal motor of fast anterograde axonal transport. Only four mutations have been identified to date.

**Objective:** To determine the frequency of SPG10 in European families with HSP and to specify the SPG10 phenotype.

**Patients and methods:** 80 index patients from families with autosomal dominant HSP were investigated for SPG10 mutations by direct sequencing of the KIF5A motor domain. Additionally, the whole gene was sequenced in 20 of these families.

**Results:** Three novel KIF5A mutations were detected in German families, including one missense mutation (c.759G>T, p.K253N), one in frame deletion (c.768_770delCAA, p.N256del) and one splice site mutation (c.217G>A). Onset of gait disturbance varied from infancy to 30 years of age. All patients presented clinically with pure HSP, but a subclinical sensory–motor neuropathy was detected by neurophysiology studies.

**Conclusions:** SPG10 accounts for approximately 3% of European autosomal dominant HSP families. All mutations affect the motor domain of kinesin and thus most likely impair axonal transport. Clinically, SPG10 is characterised by spastic paraplegia with mostly subclinical peripheral neuropathy.

Hereditary spastic paraplegia (HSP) is a clinically and genetically heterogeneous group of disorders that share the key symptom of lower extremity spasticity due to progressive degeneration of the corticospinal tract. At present, at least 52 loci for HSP, termed SPG1-37, are known, including nine genes for autosomal dominant disease.

**RESULTS**

**Sequencing of the KIF5A gene**

Mutational screening in 80 index patients revealed three novel mutations in the KIF5A motor domain, including one missense mutation (c.759G>T, p.K253N), one in frame deletion (c.768_770delCAA, p.N256del) and one splice site mutation (c.217G>A). None of these sequence variations was present in 384 unrelated control alleles. Co-segregation with the disease was shown where possible (fig 1).

Interestingly, residue N256 that is deleted by the c.768_770delCAA mutation was shown to cause HSP when replaced by serine in a British family. The c.217G>A nucleotide exchange affects a potential splice donor site and reduces splicing efficiency from 81% to 0%, as predicted by NNSPLICE 0.9.13 The effect of the c.217G>A mutation on mRNA splicing could not be tested experimentally as KIF5A is not expressed in peripheral blood and no other tissue samples were available from the affected patient.

All three novel mutations are predicted to affect protein function using programs designed to predict deleterious effects of nucleotide exchanges based on sequence homologies and physical amino acid properties (SIFT: http://blocks.fhcrc.org/sift/sift.html).

The kinesin motor domain, corresponding to amino acid residues 1–324, is highly conserved within the human kinesin family as well as...
between species (see supplementary fig 1 online). The three novel mutations found in this screen all affect highly conserved amino acid residues in the motor domain (see supplementary fig 2 online). No mutations outside the motor domain (exons 1–11) were detected in the 20 subjects in whom the whole KIF5A gene was sequenced.

SPG10 mutations were found in 3 of 41 (7%) German adHSP families. No mutations were detected in Dutch, Austrian or Serbian families. In the total cohort, the frequency of SPG10 mutations was 3/80 (4%).

Clinical description and electrophysiological characteristics of SPG10 patients

SPG10-01

The six affected members of family SPG10-01 presented with a pure form of HSP with onset of gait disturbance between early infancy and adulthood (mean age at onset 15.7 years (range 2–30)). All patients were still ambulant at the time of examination despite disease duration of more than 50 years in one family member (II-5). Three affected family members suffered from postural and action tremor of the hands consistent with the diagnosis of essential tremor that segregated independently in this family.

Apart from mild reduction of vibration sense distally in the legs, no sensory deficits were observed. Other symptoms or signs of lower motor involvement were absent. Neurophysiological examination, however, revealed subclinical peripheral neuropathy of the sensor–motor type with axonal and demyelinating features (table 1).

SPG10-02

The index patient of family SPG10-02 (II-1) developed a progressive spastic gait disturbance at 19 years of age. At age 29 years she was diagnosed with multiple sclerosis because of left-sided hemiparesis responding to cortisone pulse therapy, immunoreactive CSF syndrome and multiple hyperintense, partially contrast enhancing, predominantly periventricular but also spinal lesions on MRI. Additionally, sensory–motor neuropathy was noted. Sural nerve biopsy revealed chronic axonal neuropathy without signs of inflammation. Family history was positive with the mother also being affected by spastic gait. On examination, visual acuity was reduced on the right eye with optic atrophy on fundoscopy. Sensory deficits included impaired vibration and joint position sense. Further findings are presented in table 1.

SPG10-03

The index patient of family SPG10-03 (II-2) reported onset of a spastic gait disturbance at the age of 51 years. On inquiry, however, she recognised a Trendelenburg-like gait, particularly during running, since young adulthood. Only after replacement of both hip joints due to arthritis at the age of 51 years did this gait abnormality become more obvious in everyday life and was noted to be progressive. In addition to spastic paraplegia, subject II-2 suffered from bladder and bowel urge incontinence. No signs and symptoms of complicated disease were noted.

DISCUSSION

SPG10 was initially regarded as an infantile onset form of HSP. In agreement with two previously described SPG10 families however, our families demonstrated that age at onset is actually quite variable and ranges from early childhood until the third decade of life.

The classification of HSP into pure and complicated forms is based on clinical criteria. Using these criteria, SPG10 presents as a clinically pure form of HSP with only mild amyotrophy
were detected in Dutch, Austrian or Serbian families. K253N and N256del identified in this study, are located in the third exon of the KIF5A gene. The switch cluster, encoded by exons 9 and 10 of the KIF5A gene.

As KIF5A mutations are most likely to affect axonal transport, it is plausible that neurons with particularly long axonal processes are affected. The N256 mutations, as indicated by Reid et al, might cause decoupling of nucleotide and microtubule binding of the motor. The putative splice site mutation c.217G>A is predicted to result in omission of exon 3 which would lead to loss of the p-loop (N1) that is essential for the interaction of kinesin motor and ATP. This suggests that ATP hydrolysis and microtubule binding of KIF5A might be key targets of HSP pathogenic mutations. Pure adHSPs differ little in their clinical presentation and the discriminating features that might exist are often lost in the noise of phenotypic variability of specific adHSP subtypes. With nine dominant HSP genes known to date, containing nearly 16 kb of coding sequence, pragmatic guidelines for genetic testing are warranted. We suggest genetic testing for SPG10 in families with pure forms of HSP and onset before 45 years of age in all affected family members. Although no clusters of SPG10 mutations have been found, all private mutations identified so far are located in the kinesin motor domain.

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**Table 1 Clinical and neurophysiological features of SPG10 patients**

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>SPG10-01 II-5</th>
<th>II-10</th>
<th>III-3</th>
<th>III-9</th>
<th>III-10</th>
<th>SPG10-02 II-1</th>
<th>II-2</th>
<th>SPG10-03</th>
</tr>
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<tbody>
<tr>
<td>Age at examination (y)</td>
<td>56</td>
<td>47</td>
<td>21</td>
<td>25</td>
<td>19</td>
<td>32</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset (y)</td>
<td>2</td>
<td>30</td>
<td>21</td>
<td>4</td>
<td>15</td>
<td>19</td>
<td></td>
<td>Young adulthood</td>
</tr>
<tr>
<td>Disease duration (y)</td>
<td>54</td>
<td>17</td>
<td>0.5</td>
<td>21</td>
<td>4</td>
<td>13</td>
<td></td>
<td>&gt;30</td>
</tr>
<tr>
<td>Degree of disability*</td>
<td>(3)</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>Weakness (LL)</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
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<tr>
<td>Muscle wasting</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Spasticity (UL)</td>
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<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Spasticity (LL)</td>
<td>+</td>
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<td>Hyporeflexia (LL)</td>
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<tr>
<td>Hyporeflexia (LL)</td>
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<tr>
<td>Babinski’s sign</td>
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<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
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<tr>
<td>Impaired vibration sense (LL)</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td></td>
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<tr>
<td>Urinary urgency</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

**Neurophysiology**

| MNCV tibial nerve (N >41 m/s) | 40.0        | 33.1 | 39.9 | 36.7 | 40  |
| CMAP tibial nerve (N >10 mV)  | 2.3         | 1.0  | 4.6  | 2.2  | 22.1 |
| F latency tibial nerve (N <55 ms) | 46.7     | No F waves | 53.3 | No F waves | 51.4 |
| SNCV sural nerve (N >45 ms)   | 52          | 48   | 40   | 52   |   |
| SNAP sural nerve (N >10 μV)   | 2.1         | 1.0  | 3.2  | No SNAP | 5.9 |
| EMG TA                        | Chronic     |    |     |      |     |
| CMCT TA left/right (N <16 ms) | 21.9/23.4  | 25.8 | 25.0/29.7 | No MEP |
| CMCT FDI left/right (N <8 ms) | 8.6/8.9    | 9.0  | 9.8/10.6 | 7.8/7.8 |

*Numbering of individuals corresponds to fig 1.

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**Competing interests:** None.

**Ethics approval:** The study was approved by the local ethic committee (Vote 277/2004).

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