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We report a case of hereditary spastic paraplegia. This 38-year-old Chinese man has had lower limb weakness and spasticity for 10 years. He has normal cognition, no sensory deficits, ataxia or cataracts. There is a strong family history of spastic paraplegia. His paternal grandmother, great uncle, father, and elder brother all had weakness and spasticity. A genetic analysis showed that our patient was heterozygous for the mutation p.P361L in *SPG4*. He was diagnosed with spastic paraplegia type 4, autosomal dominant (*SPG4*, MIM#182601). About 40% of cases of hereditary spastic paraplegia are due to mutations in *SPG4* encoding for spastin, while 10% are due to mutations in *SPG3A* encoding for atlastin. To date, 38 hereditary spastic paraplegia loci and 16 hereditary spastic paraplegia-related genes have been identified. Other features include sphincter disturbance and dorsal column disturbance. Our patient may be the first case of *SPG4* confirmed by genetic analysis locally. We hope to raise clinicians' awareness of this disease and its possible molecular diagnosis.

Case report

We report a 38-year-old Chinese man (IV-2) with hereditary spastic paraplegia (HSP). He developed bilateral lower limb weakness in his late twenties and within 5 years needed to use sticks when walking. The weakness further progressed over the next 5 years until he could no longer walk and had to use a wheelchair. His cortical function remained normal all along and he works as a clerk.

A physical examination found all cranial nerves to be normal. He had normal visual fields, and a full range of eye movements with no nystagmus or diplopia. Both fundi were normal. He had no bulbar dysfunction and his swallowing ability, respiration, and speech were normal. His upper limbs were normal with full power. The lower limbs had intense spasticity with adducted posture and they were always crossing each other. The spasticity was much worse when he was under stress. The hip flexion was 3-/5 on the left side and 3/5 on the right side. The foot dorsiflexion was 3-/5 on the left side and 3/5 on the right side. All his lower limb reflexes were uniformly increased, and he had bilateral up-going plantar responses. He had normal sensation for light touch, pain, and proprioception on both lower limbs. There was no evidence of any lesion in the spinothalamic tract. He had no deafness, ataxia, epilepsy, dementia, or cataracts. Both bladder and bowel sphincters were normal and a nerve conduction study of both upper and lower limbs was normal.

Magnetic resonance imaging (MRI) of his brain showed mild cerebral atrophy, with no thinning of the corpus callosum, no midline shift, and no extra-axial collection of cerebrospinal fluid. Magnetic resonance imaging of his cervical spine and his serum vitamin B12 level were normal. He refused a lumbar puncture and a blood test for syphilitic screening.

The patient gave a strong family history of spastic paraplegia (Fig). His paternal grandmother (II-2) and his granduncle (II-3) [both now deceased], and his father (III-2) had similar symptoms. His elder brother (IV-1) also developed spastic paraplegia at a younger age but declined medical consultation. Our patient is single and has no children.

The causes of spastic paraplegia can be broadly divided into acquired and hereditary causes.¹ Acquired causes of spastic paraplegia include spinal cord compression by various processes, 'inflammatory' causes such as multiple sclerosis, human immunodeficiency virus, and human T-cell lymphotropic virus type 1 infections, and acquired metabolic diseases like vitamin B12 and folate deficiencies. Hereditary causes include HSP and some inborn errors of metabolism such as adrenoleukodystrophy and arginase deficiency.

Taken together, the patient's clinical picture and strong family history suggested autosomal dominant HSP. We analysed his *SPG4* gene for mutations and offered the family genetic counselling. Peripheral blood samples were collected from our patient (IV-2) and his father (III-2) after informed consent. His elder brother (IV-1) declined both a medical consultation and genetic testing. Genomic DNA was extracted using a QIAamp Blood Kit (Qiagen, Hilden, Germany). The coding exons and the flanking introns of the

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遺傳性痙攣性截癱

本文報告遺傳性痙攣性截癱一例。一名38歲男子下肢無力及痙攣長達10年，他認知功能正常，並無感覺神經缺陷、共濟失調或白內障。病人有強烈的痙攣性截癱家族病史，他祖母、舅公、父親和兄長均出現無力及痙攣。遺傳學分析顯示病人的SPG4基因p.P361L突變呈異合性，被診斷為常染色體顯性痙攣性截癱4型（SPG4，MIM#182601）。遺傳性痙攣性截癱約有四成病例由spastin基因SPG4突變引起，另有一成因atlastin基因SPG3A突變而造成。目前已發現與遺傳性痙攣性截癱有關的38個基因位點及16種基因。其餘徵狀有括約肌失調和脊柱失調。這可能是本地首宗由遺傳學分析確診的SPG4病例。我們希望藉此提高醫生對這種病的警覺性及對這種病的分子分析。

sequencing kit (Applied Biosystems, Foster City [CA], US). Our patient and his father were found to be heterozygous for a known disease-causing mutation, p.P361L, in *SPG4*.² They were thus diagnosed with spastic paraplegia type 4, autosomal dominant (SPG4, MIM#182601).

Discussion

Hereditary spastic paraplegia is a heterogeneous group of genetic disorders characterised by progressive weakness and spasticity of the lower limbs, due to pyramidal tract dysfunction.³ It is a genetically heterogeneous disease and can be inherited via an autosomal dominant, autosomal recessive or X-linked gene. Of autosomal dominant HSP cases, which account for 70 to 80% of all HSP cases, 40% are due to mutations in the gene for spastin (*SPG4*) while 10% are due to mutations in *SPG3A* encoding for atlastin.⁴ In autosomal recessive HSP, *SPG11* is the most frequent form and represents 41 to 77% of all cases of autosomal recessive HSP with a thin corpus callosum.³ Today, at least 38 HSP loci and 16 HSP-related genes have been identified.³

Hereditary spastic paraplegia can be classified into pure or complicated forms.⁵ In the pure form, the clinical features include spasticity and hyperreflexia of the lower limbs, gait disturbance plus extensor plantar responses. Other common features include: paresis of the lower limbs, sphincter disturbance, mild dorsal column disturbance, hyperreflexia of the upper limbs, mild terminal dysmetria, and loss of ankle reflexes.⁵ In the complicated form, there are additional neurological signs like ataxia, deafness, cataracts, epilepsy, dementia, etc.⁶

The progressive lower limb weakness and spasticity seen in HSP are caused by degeneration of the terminal axons in the cortico-spinal tracts and dorsal columns of the spinal cord.⁷ *SPG4* is the gene for spastin which is a member of the 'ATPases associated with diverse cellular activities' (AAA) protein family.⁷ Spastin has two domains: one at the N-terminus and the other at the C-terminus. The microtubule interacting and endosomal trafficking domain is at the N-terminus and the AAA domain is at the C-terminus. Spastin can interact with microtubules, just like katanin, which is also a member of the AAA. Spastin has microtubule-severing activity and is able to 'bundle' microtubules in vitro and is essential for normal neuronal function. Mutant spastin disrupts the normal cellular trafficking of the microtubule-dependent intracellular organelle, and the transduction of messages from neuronal axons and myelinating cells.⁷

The molecular mechanisms by which the different forms of HSP lead to axonal degeneration are diverse, including axonal transport dysfunction,

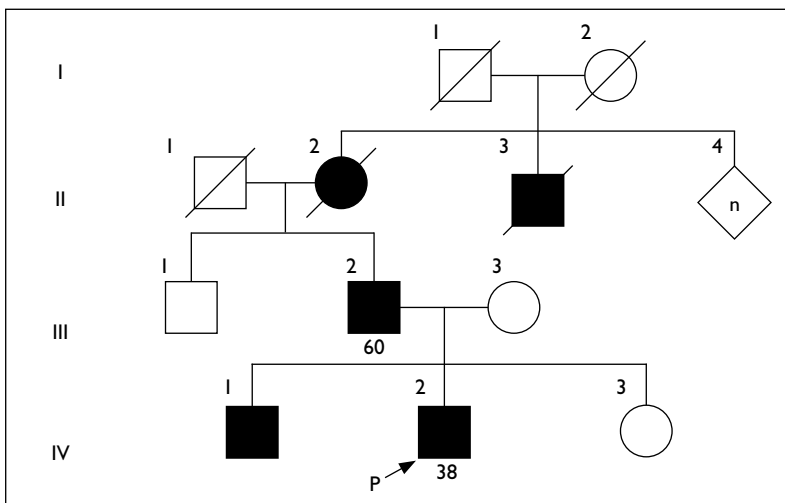


FIG. Pedigree of the reported family with spastic paraplegia type 4, autosomal dominant (SPG4)

The age (years) indicates the age at the time of genetic testing; the 'n' and the rhomboid represent the uncertain number and sex of siblings, respectively; the 'P' stands for the proband

SPG4 gene were amplified using a polymerase chain reaction (PCR; primer sequences are available upon request). The numbering of nucleotides is based on GenBank accession number NM_014946.3 with 617 amino acids. Amplification was performed using the touch-down method: 94°C for 12 minutes, 10 cycles of 94°C for 30 seconds, 59°C for 30 seconds (the temperature was lowered 1°C for each cycle), 72°C for 30 seconds; 30 cycles of 94°C for 45 seconds, 53°C for 30 seconds, 72°C for 30 seconds, and a final extension at 72°C for 8 minutes. The reaction mixture (final volume 20 µL) contained 10X PCR buffer (Qiagen, Hilden, Germany), 5X Q-solution (Qiagen, Hilden, Germany), 2 mM of magnesium chloride, 200 µM of dNTP, 1 µM of each primer, 0.625 units of HotStarTaq DNA polymerase (Qiagen, Hilden, Germany), and 50 ng of DNA template. The PCR products were sequenced directly using a BigDye Terminator cycle

demyelination, mitochondrial dysfunction, and others. The fibres innervating the lower extremities are most vulnerable because of their long lengths.^{3,7}

Differentiating HSP from other diseases is clinically challenging. Firstly, the symptoms of SPG4 can present at any age. Although the mean age at onset of SPG4 is 30 years, the age of onset can vary from infancy to the eighth decade, even in the same family.^{3,8} Secondly, about 25% of patients carrying the mutation in HSP-related genes can be asymptomatic.⁹ Thirdly, the *SPG4* phenotype can be modified by polymorphism in other genes. The p.G563A polymorphism in the gene encoding heat shock protein 60 (*HSP60*) appears to interact with *SPG4*, resulting in an earlier onset phenotype.¹⁰ These findings explain the necessity of careful examination even in asymptomatic family members.⁹ It also explains the difficulty of defining the exact time of symptom onset, especially in patients who have had the symptoms for decades.¹¹

Harding⁵ suggested that pure HSP be classified into two groups: type I and type II. Type I, describing people with symptom onset before the age of 35 years, is associated with a slower and more variable course, whereas type II, encompassing those with symptom onset after the age of 35 years, is associated with a more rapid course and more severe weakness, sphincter disturbance, and sensory loss.⁵

In patients who have weakness and wasting of both upper limbs, distal hereditary motor neuropathy type V (dHMN-V) should be considered.⁴ This is an unusual autosomal dominant disorder, which is a variant of the neuronal form of Charcot-Marie-Tooth (CMT) disease. If sensory loss is present, it is called hereditary motor and sensory neuropathy or a variant of CMT disease type 2.⁴ In contrast to HSP, dHMN-V patients usually start with weakness in both upper limbs rather than spasticity and weakness in the lower limbs.

Although the majority of SPG4 patients present with pure HSP, a complicated phenotype with progressive bulbar dysfunction and respiratory failure has been reported.⁷ Missense mutations p.S44L and p.P45Q, when co-segregated with another mutation in *SPG4*, were reported to exert a phenotype-modifying effect, leading to an earlier age of onset and a more severe phenotype.⁷ It is therefore important to screen the whole gene because of the possibility of double mutations and intragenic modifiers.⁷

Hereditary spastic paraplegia caused by *SPG4* gene mutations has been reported in Chinese patients. Qin et al¹² reported the first case of *SPG4* mutation in Chinese: a novel insertion mutation

was identified in 20 patients with spastic paraplegia in a large, 47-member family. The mutation was c.1485_1486insGG, numbered according to Ensembl transcript ID ENST00000345662 counting the first nucleotide from 125 nucleotides upstream from the starting codon ATG, or c.1360_1361insGG based on GenBank accession number NM_014946.3 counting the first nucleotide from the starting codon ATG. Tang et al¹³ identified three novel mutations (p.L378Q, p.M390V, c.1543_1545delCTA based on NM_014946.3) of *SPG4* in four out of 22 Chinese families. The last deletion would be c.1668_1670delCTA if Ensembl transcript ID ENST00000345662 is used. They concluded that the percentage of *SPG4* mutations in Chinese autosomal dominant HSP patients (18%) is lower than estimated. The study covered mutations only, not exon deletions, hence the percentage could have been underestimated. We are not aware of any cases of SPG4 being reported locally and believe our case is the first case to be reported in Hong Kong. The prevalence in other countries can vary due to differing diagnostic criteria, variable epidemiological methods, and different catchments within the geographical areas. The reported prevalence in Molis, Italy was 2.7 in 100 000 whereas that reported in Portugal was 2.0 in 100 000.^{14,15}

Hereditary spastic paraplegia should be suspected in patients with typical clinical features and a positive family history. Genetic tests can be performed after the exclusion of structural and metabolic causes of spastic paraplegia. Appropriate genetic testing for different forms of HSP should be selected based on the clinical information, radiological findings, and modes of inheritance in each patient. For example, genetic testing for *SPG4* could be considered first in patients with adult-onset pure-form autosomal dominant HSP; *SPG3A* should be sought in those with young-onset pure-form autosomal dominant HSP; and *SPG11* in those with the complicated form of autosomal recessive HSP associated with a thin corpus callosum on cerebral MRI. Some more common HSP, such as SPG4, may also account for 10 to 15% of apparently sporadic cases.³ Genetic tests for *SPG4*, *SPG3A*, and *SPG11* are now available locally (<http://kwcpath.home/genetics>).

Treatments are mainly supportive, including drugs to lessen the lower limb spasticity, anticholinergic drugs for urinary urgency, physiotherapy, walking aids, and psychological and social support. There is no therapeutic treatment available for HSP at present. Our case may be the first case of SPG4 confirmed by genetic analysis locally. We hope to raise awareness among clinicians about this disease and the available molecular diagnostics.

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