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## Spinocerebellar ataxia type 6

### 脊髓小腦共濟失調6型

We report a 39-year-old woman with spinocerebellar ataxia type 6. She presented with ataxia and a 3-year history of progressive ataxia and recurrent falls. There was no relevant family history. Genetic tests revealed an expanded allele of 24 CAG repeats at the spinocerebellar ataxia type 6 locus. This appears to be the first case reported in Hong Kong. As genetic testing becomes more widely available and clinical awareness increases, more such patients are expected to be diagnosed.

本文描述一名39歲女性所患的脊髓小腦共濟失調6型。患者有共濟失調的徵狀，患上漸進式共濟失調已三年，期間曾反覆跌倒，家族中從未有患同類型的疾病。基因測試發現，染色體中脊髓小腦共濟失調6型基因編碼區出現24CAG等位基因重複序列擴展。這情況在香港屬首次發現。由於基因測試日趨普及，加上醫護人員對這種疾病的警覺性越來越高，相信診斷患上本症的病人會越來越多。

### Introduction

Spinocerebellar ataxia type 6 (SCA6; OMIM 183086) is a mild form of the autosomal dominant spinocerebellar ataxias (SCAs), and is clinically characterised by slowly progressive ataxia of the limbs and gait, dysarthria, nystagmus, incoordination, and impaired sensations of vibration and proprioception. It is caused by a small CAG repeat expansion in the gene coding for the  $\alpha_{1A}$ -voltage-dependent P/Q-type calcium channel subunit (CACNA1A) on chromosome 19p13. This chromosome is important for normal Purkinje cell function and survival.<sup>1-3</sup> Normal alleles have 4 to 18 CAG repeats, whereas expanded alleles have 20 to 33.

### Case report

The patient was a 39-year-old woman who came to Hong Kong from Guangdong, China in 1996. She was married with a 14-year-old son and had enjoyed good health until 2001 when she started experiencing recurrent falls. Magnetic resonance imaging showed cerebellar atrophy and nerve conduction studies revealed mild motor demyelinating polyneuropathy. Cerebrospinal fluid examination was normal (protein, 0.28 g/L; glucose, 3.7 mmol/L), as was high cortical function. There was no nystagmus or diplopia, and speech and fundi were normal. All four limbs had full power (5/5), both proximally and distally. On referral to the author's hospital there was marked cerebellar ataxia with clumsiness of all limbs. There was no vertical or horizontal nystagmus and all jerks were slightly brisk. There were no upper motor neuron signs, and no clonus or up-going plantar responses. Sensation to light touch, pain, and proprioception were normal. There was no family history (over four generations) of ataxia or clumsiness. The son was not tested. Genetic tests for SCA type 1, 2, 3, 6, 7, 8, 12, 17 and dentatorubral-pallidolucylian atrophy (DRPLA) were performed as previously described.<sup>4</sup> Results showed that the patient was heterozygous with one normal and one expanded CAG repeat alleles (13

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#### 關鍵詞：

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and 24, respectively) at the SCA6 locus. All other SCA tests were negative. Direct sequencing was performed to accurately determine the size of the expanded allele. Autosomal dominant SCA6 was confirmed.

## Discussion

The dominantly inherited SCAs are a heterogeneous group of neurological disorders characterised by variable degrees of degeneration of the cerebellum, spinocerebellar tracts, and brain stem neurons. The genes for SCA1 and SCA6 were identified in 1993 and 1997 respectively.<sup>1,5</sup> The author's hospital introduced genetic testing for the disorders in March 2001. New genetic loci for other SCAs continue to be discovered and more genetic tests are available. A negative 'SCA screening' result cannot exclude a currently unidentified SCA. There is phenotypic variation in this heterogeneous group of diseases, thus genetic tests are essential for an accurate diagnosis. The prevalence of SCA6 is approximately 0.02 to 0.31 per 100 000 population,<sup>6,7</sup> although the frequency varies in different countries. In the United States, SCA6 comprises 12% of all SCAs.<sup>6</sup> In Tottori Prefecture, Chugoku, and Kansai of Japan, it comprises up to 25% of all SCAs.<sup>8,9</sup> In Taiwan, 10.8% (second to SCA3 which is 47.3%) of all SCAs are SCA6.<sup>10</sup> In Singapore, 5% of all SCAs are SCA6.<sup>11</sup> In Germany and France, the percentages are 13% and 2%, respectively.<sup>12,13</sup> The prevalence in Mainland China may be similar to that of Taiwan (10.8% SCA6 of all SCAs) since immigrants from the former comprise a large percentage of inhabitants in Taiwan.<sup>14</sup> However precise prevalence data are not available. An Australian study revealed the absence of SCA6 in patients of Chinese descent.<sup>15</sup> In Taiwan, there was a geographic cluster of families with SCA6<sup>10</sup>; this suggests a founder effect in SCA6 patients, and has also been reported in Japan and Germany.<sup>9,16</sup>

There is an inverse relationship between the size of CAG expansion and the age of onset.<sup>6,7,12,13</sup> An earlier onset of disease with more severe clinical manifestations is seen in patients who are compound heterozygous and homozygous for expanded CAG repeats. This suggests a gene-dosage effect.<sup>6,7,10</sup> One striking feature of SCA6 is the stability of its CAG repeats over subsequent generations.<sup>10</sup> Nonetheless phenotypic presentation and age of onset vary widely in the presence of a consistent number of CAG repeats, even within one family.<sup>6,7,10,13,17-19</sup> Other unidentified mechanisms may determine clinical outcome.<sup>13,19</sup>

All SCAs share two features: expansion of the polyglutamine tract and accumulation of the mutant

protein.<sup>1</sup> There is a gain-of-function mechanism due to increased CAG repeats whereby the mutant protein becomes toxic to neurons. Studies of transgenic animal models for DRPLA have shown that intranuclear accumulation of mutant protein results in neuronal dysfunction. Nuclear proteins that interact with expanded polyglutamine stretches may be involved in the pathogenesis of polyglutamine diseases.<sup>20</sup> There are two key differences between SCA6 and other polyglutamine diseases<sup>1</sup>: the expansion in SCA6 alleles is much smaller and the CAG expansion occurs in the coding region of a gene that is important for normal Purkinje cell function and survival. CAG expansion in SCA6 may have a direct pathogenic effect on the function of  $\alpha_{1A}$ -calcium channels.<sup>1,17,21</sup>

Gait ataxia in adulthood is the most common presenting symptom of SCA6 and it has a slow progressive course. Other features include unsteadiness, ataxia, incoordination, tremor, dysarthria, horizontal or vertical nystagmus, dysphagia and choking, hyper-reflexia, and extensor plantar responses. The clinical picture is nonetheless inconsistent.<sup>7,9,13,14</sup> High cortical function is usually intact and life span is not affected.<sup>17,18</sup> Age of onset varies from 19 to 72 years of age, but is usually between 43 and 52 years of age.<sup>17,18</sup> There are no diagnostic features specific for SCA6. Accurate diagnosis therefore depends on genetic testing.<sup>10,14</sup> In SCA6, there are 14 to 18 CAG repeats in normal alleles. Overall heterozygosity is 76.5%.<sup>10</sup> The most common repeat numbers are 11 and 13.<sup>1,3,7</sup> Expanded alleles have a repeat size of 20 to 33: the most common is 22.<sup>1,3,7</sup> Spinocerebellar ataxia type 6 alleles with 19 repeats are considered intermediate and not thought to be pathogenic since asymptomatic heterozygous individuals with 19 CAG repeats have been reported.<sup>1,19</sup> Most, but not all, affected patients have an affected parent.<sup>7</sup> The lack of a family history may be due to late manifestation of the disease in apparently healthy parents. De-novo gene mutation may occur but the incidence is unknown.<sup>13,17,19,21</sup>

Spinocerebellar ataxia type 6 is allelic to two other autosomal dominant disorders that are also due to point mutations in the CACNA1A gene: familial hemiplegic migraine (FHM) and episodic ataxia type 2 (EA-2).<sup>22</sup> Familial hemiplegic migraine commonly presents with headache, nystagmus, cerebellar ataxia, and aura symptoms such as hemiplegia, hemianopsia, and hemisensory deficit. Episodic ataxia type 2 is episodic in its early stages with clinical features of ataxia, vertigo, tinnitus, dystonia, hemiplegia, and headache. Onset is usually before the age of 20 years. Episodes can be precipitated by physical exertion and emotional

stress. Spinocerebellar ataxia type 6 cannot be differentiated from FHM and EA-2 on clinical grounds and genetic tests are necessary. Interestingly, a Japanese study showed that five patients with SCA from two families had a large SCA8 CTA/CTG repeat coexistent with a large SCA6 CAG repeat expansion.<sup>23</sup> There is no treatment for SCA6 although acetazolamide has been reported to stabilise early stage EA-2 by stabilising the transient dysfunction in the mutant calcium channels.<sup>22,24</sup> Genetic counselling and advice about family planning are important for patients with SCA6. Autosomal dominant disorders are characterised by vertical transmission of the disease with equal clinical expression in males and females. When one parent is affected, any offspring have a 50% chance of acquiring the gene. The possibility of transmitting the disease allele varies for heterozygous and homozygous individuals but homozygous individuals for a dominant disease are relatively rare. Patients should receive social and psychological support, advice before pregnancy, prenatal testing, and the opportunity to discuss options for continuing or discontinuing a pregnancy should the foetus be found affected. Genetic testing of at-risk children remains a controversial medical and legal issue, especially when there is no treatment for the screened disease.<sup>25,26</sup> The interest of the children should be the first consideration.

This patient appears to be the first reported case in Hong Kong. This report aimed to raise awareness among local clinicians so that patients with SCA6 receive appropriate medical attention early on. A clearer idea of the prevalence of SCA6 in Hong Kong will also evolve.

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