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Novel mutations of the *SPG11* gene in hereditary spastic paraplegia with thin corpus callosum

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ABSTRACT

Background: Hereditary spastic paraplegia with thin corpus callosum (HSP–TCC) is a clinically and genetically heterogeneous neurodegenerative disorder with genetic linkage to multi-loci. Recently pathogenic mutations in the *KIAA1840* (now named *SPG11*) for *SPG11*, the major HSP–TCC locus, were identified; at least 42 different mutations have been detected.
Objective: To study the clinical features and identify the *SPG11* gene mutations in Chinese patients with HSP–TCC.
Methods: Three kindreds with an autosomal recessive HSP–TCC and 5 cases with sporadic HSP–TCC in Chinese Hans were recruited. Detailed clinical history, neurological examination, MRI, electromyography, Mini Mental State Examination (MMSE), Spastic Paraplegia Rating Scale (SPRS) were presented. DNA samples of the 8 families were collected and mutation analysis of *SPG11* gene was carried out by direct DNA sequencing.
Results: Except for one patient whose age at onset was 3 years old, 10 patients manifested a relatively similar combination of adolescence-onset cognitive decline and spastic paraparesis with TCC on brain MRI. We identified 10 novel and one known mutations in our 8 HSP–TCC families, which were two nonsense mutations (c.5977C>T/p.Q1993X, c.4668T>A/p.Y1556X), three small deletions (c.6898_6899delCT/p.L2300AfsX2338, c.3719_3720delTA/p.I1240VfsX263, c.733_734delAT/p.M245VfsX246), four small insertions (c.7088_7089insATTA/p.Y2363X, c.2163_2164insT/p.I722YfsX731, c.7101_7102insT/p.K2368X, c.6790_6791insC/p.L2264PfsX2339), one deletion/insertion (c.654_655delinsG/p.S218RfsX219), and one splice mutation (c.7151+4_7151+7delAGTA/p.K2384fsX2386). Each family has a different mutation and all the mutations are predicted to cause early protein truncation.
Conclusion: This study widens the mutation spectrum of the *SPG11* gene and the mutations in the *SPG11* gene are also the major causative gene for HSP–TCC in the Chinese Hans. Screening of the whole gene is recommended in clinical practice.

1. Introduction

Hereditary spastic paraplegia (HSP or spastic paraplegia SPG) is a group of clinically and genetically heterogeneous neurodegenerative disorders characterized by slowly progressive weakness and spasticity of the lower limbs. According to clinical manifestation, HSP is classified into "pure", when spasticity occurs in isolation and "complicated" forms, when additional neurological manifestations are present, which include ophthalmoplegia, atrophia nervi optici, pigmentary degeneration of retina, dysarthria, dysphagia, cerebellar signs, extrapyramidal signs, amyotrophy, peripheral neuropathy, dementia, skeletal deformity, cavus, and dermatopathy [1,2]. According to the inheritance mode, HSP is divided into autosomal dominant, [3] recessive, [4] and X-linked forms [5]. So far, at least 39 distinct HSP loci designated SPG have been assigned with 17 disease-associated genes identified [6,7].

Hereditary spastic paraplegia with thin corpus callosum (HSP–TCC) is the most common type of complicated HSP characterized by slowly progressive spastic paraparesis and mental retardation, onset within the second decade of life, most with autosomal recessive inheritance

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(ARHSP–TCC; OMIM: 604360). Additional symptoms include occasional seizures, peripheral neuropathy, cerebellar ataxia, extrapyramidal signs, and skeletal deformity. Brain magnetic resonance imaging (MRI) shows remarkable thinning of the corpus callosum [8–10]. Since originally described in four Japanese patients from the two different families by Nakamura et al., [8] HSP–TCC has also been reported in many other countries [11–18], and confirmed to have a worldwide distribution. It is also a clinically and genetically heterogeneous disorder with genetic linkage to chromosome 15q13–15 (*SPG11*) in most affected families, [13,16–19] and chromosome 8 [20], chromosome 16 [11] and other unknown loci [16,18] in the rest. Moreover, TCC has also been associated with other forms of HSP, including those linked with SPG4 (spastin), [21] SPG7 (paraplegin), [11] and SPG21 (maspardin) [22].

In the previous studies, we recruited 3 kindreds with an autosomal recessive HSP–TCC and 5 sporadic HSP–TCC cases. All patients in the 8 families presented here had analogous manifestations, including onset at the age of adolescence (except one at infancy), slowly progressive spastic paraparesis, moderate to severe cognitive impairments, and thin corpus callosum [23]. To find out the causative gene for these patients, polymerase chain reaction–single strand conformation polymorphism (PCR–SSCP) and direct sequencing were carried out, however, no mutation was detected in spastin, paraplegin, or maspardin genes [10,14–15].

Recently mutations in the *SPG11* gene, that encodes spatacsin, were identified as the major cause of ARHSP–TCC. The *SPG11* gene contains 40 exons, and its full-length 8-kb transcript encodes a predicted protein of 2443 amino acids of unknown function [24]. Spatacsin might have an essential biological function because it is expressed ubiquitously and is highly conserved among species [24]. The possible presence of at least one transmembrane domain suggests it might be a receptor or transporter [24]. To date, at least 42 different mutations of the *SPG11* gene were identified, and all were predicted to cause early protein truncation of spatacsin, [24–28]. suggesting a possible loss-of-function mechanism.

We presumed that *SPG11* gene may be the causative gene for our 8 HSP–TCC families. Then, we analyzed the *SPG11* gene mutation in the probands by direct sequencing of all 40 exons and their splicing sites, and 10 novel *SPG11* gene mutations and one previously reported were found among them (Fig. 1).

2. Materials and methods

2.1. Patients

Six patients with autosomal recessive HSP–TCC from 3 families and 5 cases with sporadic HSP–TCC were recruited. The study was

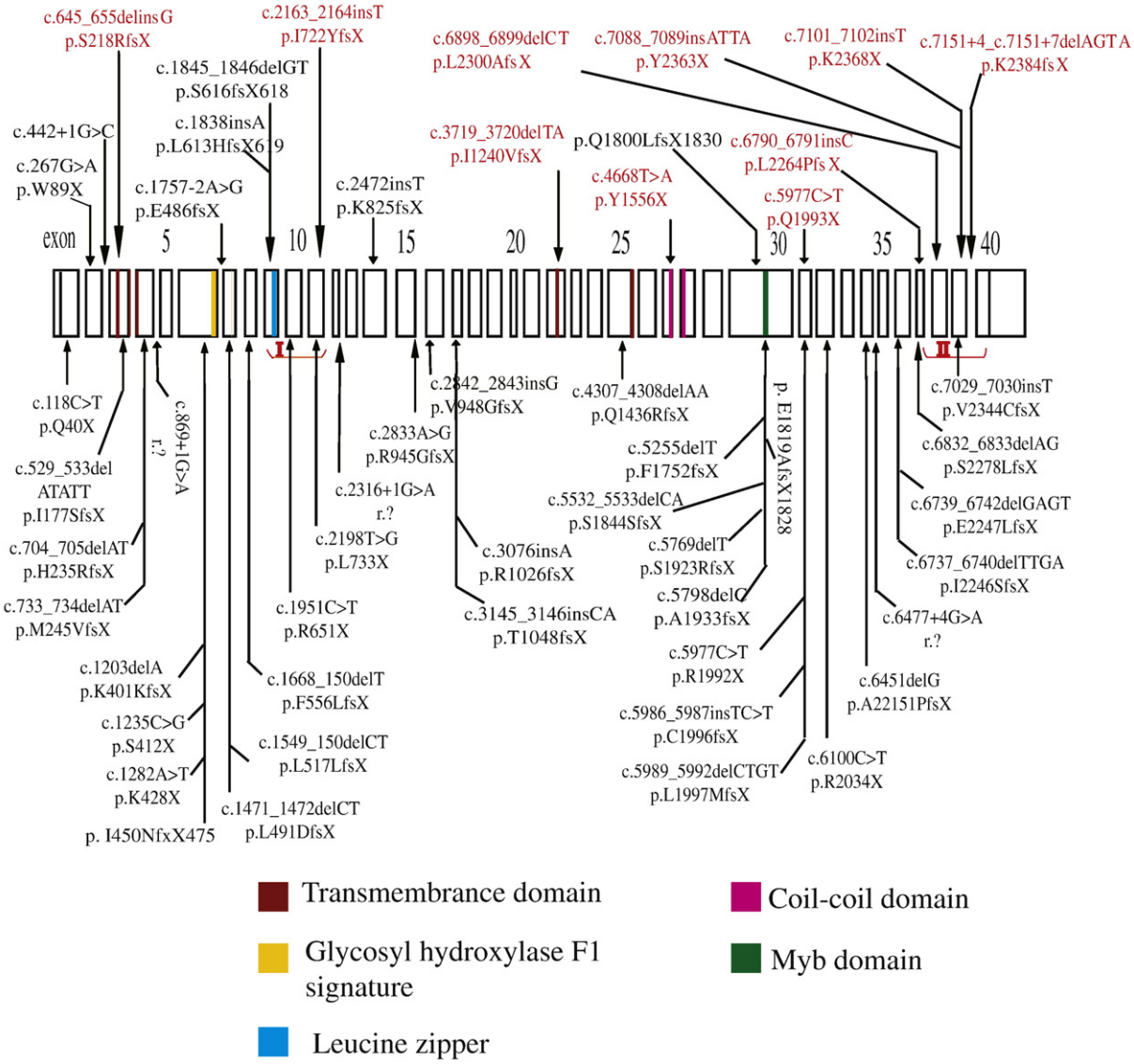

Fig. 1. Schematic representation of mutation spectrum and complementary DNA (cDNA) of *SPG11* gene. The nucleic acid sequence encoding the function domains of spatacsin are indicated in different colors. The novel and known mutations identified in this study are indicated in red and bold respectively. The function domains of spatacsin are confined by Stevanin [24].