ORIGINAL ARTICLE

Novel *SPG 11* Mutations in Hereditary Spastic Paraplegia With Thin Corpus Callosum in a Chinese Family

Xiaojie Tian, Min Wang, Kaiyuan Zhang, Xinqing Zhang

ABSTRACT: ***Background:*** Hereditary spastic paraplegia (HSP) is a neurodegenerative disease that is characterized by progressive weakness and spasticity of the lower extremities; HSP can present as complicated forms with additional neurological signs. More than 70 disease *loci* have been described with different modes of inheritance. ***Methods:*** In this study, nine subjects from a Chinese family that included two individuals affected by HSP were examined through detailed clinical evaluations, physical examinations, and genetic tests. Targeted exome capture technology was used to identify gene mutations. ***Results:*** Two novel compound heterozygous mutations in the *SPG 11* gene were identified, c.4001_4002insATAAC and c.4057C > G. The c.4001_4002insATAAC mutation leads to a reading frame shift during transcription, resulting in premature termination of the protein product. The missense mutation c.4057C > G (p.H1353D) is located in a highly conserved domain and is predicted to be a damaging substitution. ***Conclusions:*** Based on the results described here, we propose that these novel compound heterozygous mutations in *SPG 11* are the genetic cause of autosomal recessive HSP in this Chinese family.

RÉSUMÉ: Nouvelles mutations SPG 11 chez une famille chinoise atteinte de paraplégie spastique avec corps calleux aminci. ***Contexte*** : La paraplégie spastique héréditaire (PSH) est une maladie neurodégénérative caractérisée par une faiblesse et une spasticité progressives des membres inférieurs. Il en existe des formes plus complexes comportant des signes neurologiques additionnels. Plus de 70 locus responsables de cette maladie ainsi que différents modes d'hérédité ont été rapportés. ***Méthodologie*** : Cette étude a porté sur 9 sujets d'une famille chinoise dont 2 individus étaient atteints de PSH. Ils ont subi des évaluations cliniques, des examens physiques ainsi que des tests génétiques détaillés. Nous avons utilisé la technique de capture ciblée des exomes pour identifier les mutations génétiques. ***Résultats*** : Deux nouvelles mutations dans le gène SPG 11, présentes dans cette famille à l'état hétérozygote composé, ont été identifiées, c.4001_4002insATAAC et c.4057C>G. La mutation c.4001_4002insATAAC induit un décalage du cadre de lecture pendant la transcription entraînant ainsi la production d'une protéine tronquée. La mutation faux sens c.4057C>G (p.H1353D) est située dans un domaine hautement conservé, ce qui devrait s'avérer une substitution néfaste. ***Conclusions*** : En nous basant sur ces résultats, nous proposons que ces nouvelles mutations du gène SPG 11, présentes dans cette famille chinoise à l'état hétérozygote composé, sont la cause génétique de la PSH autosomique récessive dans cette famille.

Keywords: Genetics, Hereditary spastic paraplegia, Mutation, Targeted exome capture, Thin corpus callosum, *SPG 11*

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Hereditary spastic paraplegia (HSP) is a clinically and genetically heterogeneous disorder that involves progressive weakness and spasticity of the lower extremities followed by a similar decline in the upper extremities.[1] Clinically, HSP is divided into two forms: the pure form variant demonstrates spasticity as the major presenting feature, whereas the complex variant exhibits additional symptoms including ataxia, mental retardation, peripheral neuropathy, muscle atrophy, and/or dysarthria.[2,3] Genetically, HSP can also be classified according to the pattern of inheritance, which can be autosomal recessive, autosomal dominant, X-linked recessive, and sporadic. Autosomal recessive HSP with thin corpus callosum (ARHSP-TCC) is one form of this disease, and alterations of the *SPG 11* gene account for 41% to 77% of ARHSP-TCC cases.[4,5] In the current study, members of a Chinese HSP pedigree were clinically and genetically examined to characterize the phenotype and to identify the genotype. We identified a novel compound heterozygous mutation in the *SPG 11* gene by using a combined approach that included targeted exome capture technology and candidate mutation validation.

Materials and Methods

Ethics Statement

The use of clinical information and human-derived materials in this study was approved by the Ethical Committee of Xuan Wu Hospital, Capital Medical University. Written informed consent

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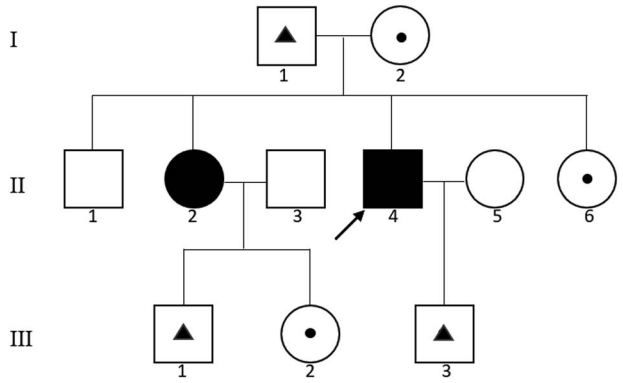

Figure 1: *Pedigree of the family. Squares indicate males; circles, females; arrow, proband; solid symbols, affected individual; small triangle with square or circle, c.4001_4002insATAAC mutation carrier; small dot with square or circle, c.4057C > G mutation carrier.*

was obtained from all subjects or from the parents or legal guardians of minor subjects.

Subjects

The pedigree chart is illustrated in Figure 1. A detailed medical history was obtained from nine individuals, including two patients (II-2, II-4) and seven family members (I-1, I-2, II-1, II-6, III-1, III-2, and III-3). All of these individuals were physically examined by two experienced neurologists (MW, XZ) and underwent genetic testing. The proband was a young man (II-4), and the other patient was his older sister (II-2). Other family members (including the patients' parents, siblings, and children) had normal clinical presentations. The patients were not the products of a consanguineous relationship. Detailed information regarding the age of onset, the progression of disability, and the clinical manifestation was obtained. Mental impairment was measured by the Wechsler Adult Intelligence Scale-Revised

Table 1: HSP-associated genes included in the clinical screening panel

Subtype	Gene	Mode of Inheritance	Subtype	Gene	Mode of Inheritance
SPG 1	*L1CAM*	XR	*SPG 49*	*TECPR2*	AR
SPG 2	*PLP1*	XR	*SPG 50*	*AP4M1*	AR
SPG 3	*ATL1*	AD	*SPG 51*	*AP4E1*	AR
SPG 4	*SPAST*	AD	*SPG 52*	*AP4S1*	AR
SPG 5	*CYP7B1*	AR	*SPG 53*	*VPS37A*	AR
SPG 6	*NIPA1*	AD	*SPG 54*	*DDHD2*	AR
SPG 7	*PGN*	AR	*SPG 55*	*C12orf65*	AR
SPG 8	*KIAA0196*	AD	*SPG 56*	*CYP2U1*	AR
SPG 10	*KIF5A*	AD	*SPG 57*	*TFG*	AR
SPG 11	*SPG 11*	AR	*SPG 58*	*KIF1C*	AR
SPG 12	*RTN2*	AD	*SPG 59*	*USP8*	AR
SPG 13	*HSPD1*	AD	*SPG 60*	*WDR48*	AR
SPG 15	*ZFYVE26*	AR	*SPG 61*	*ARL6IP1*	AR
SPG 17	*BSCL2*	AD	*SPG 62*	*ERLIN1*	AR
SPG 18	*ERLIN2*	AR	*SPG 63*	*AMPD2*	AR
SPG 20	*SPG 20*	AR	*SPG 64*	*ENTPD1*	AR
SPG 21	*SPG 21*	AR	*SPG 66*	*ARSI*	AR
SPG 22	*SLC16A2*	XR/XD	*SPG 67*	*PGAP1*	AR
SPG 26	*B4GALNT1*	AR	*SPG 68*	*FLRT1*	AR
SPG 28	*DDHD1*	AR	*SPG 69*	*RAB3GAP2*	AR
SPG 30	*KIF1A*	AR	*SPG 70*	*MARS*	AR
SPG 31	*REEP1*	AD	*SPG 71*	*ZFR*	AR
SPG 33	*ZFYVE27*	AD	*SPG 72*	*REEP2*	AR
SPG 35	*FA2H*	AR	*SPG*	*MAG*	AR
SPG 39	*PNPLA6*	AR	*SPG*	*BICD2*	AR
SPG 46	*GBA2*	AR	*SPG*	*LYST*	AR
SPG 47	*AP4B1*	AR	*SPG + HSN*	*CCT5*	AR
SPG 48	*KIAA0415*	AR	*SPG + HSN*	*FAM134B*	AR

AD = autosomal dominant inheritance; AR = autosomal recessive inheritance; XD = X chromosome dominant inheritance; XR = X chromosome recessive inheritance.

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Table 2: The sequence of PCR primers and expected PCR product size

Target Region	Primer Sequence	Product Size (bp)	Tm (°C)
Exon 24	Forward: TTAGTGGCTTACCTCTGC Reverse: AGCGAAACTCTGTCTCAA	375	58

in China (WAIS-RC). Magnetic resonance imaging (MRI), electromyogram (EMG) and cerebrospinal fluid (CSF) analysis were performed for both patients.

Mutation Analysis

Screening for Mutations

Blood samples were collected from all nine family members. We then extracted genomic DNA according to the manufacturer's instructions (D2492 Blood DNA Maxi Kit, Omega Bio-Tek, Norcross, GA). Based on targeted exome capture technology, a specific HSP panel was generated and used to collect the protein coding regions of 56 targeted genes (Table 1). Next, we prepared exon-enriched DNA libraries for high-throughput sequencing using the Illumina HiSeq 2000 platform. Initially, targeted exome sequencing was performed on the proband. A mean exome coverage of more than 98.1% was obtained, with a variant accuracy of more than 95%. These changes were computationally filtered against exome data from ethnic Han Chinese in Beijing, available through the 1000 Genomes Project (http://www.1000genome.org), against the Han Chinese Beijing SNPs in dbSNP131, the National Heart, Lung, and Blood Institute GO Exome Sequencing Project (http://evs.gs.washington.edu/EVS/), and the data from 5,038 in-house subjects (from the Beijing Genomics Institute, Shenzhen, China).

Mutation Validation

The variants identified in the proband were confirmed by direct polymerase chain reaction product sequencing using Bigdye terminator V3.1 cycle sequencing kits (Applied Biosystems, Foster City, CA) and analyzed on an ABI 3130XL genetic analyzer. Whether the variants that were detected by targeted exome sequencing co-segregated with the disease phenotype in the family was tested by Sanger sequencing. Primer pairs were designed using a primer program (http://www.yeastgenome.org/cgi-bin/web-primer) (DNA reference number NG_009759) (Table 2).

Results

Clinical Data

The proband (II-4) was a 29-year-old male who suffered from progressive weakness and stiffness of the lower extremities for 5 years and experienced a similar decline in the upper extremities for 1 year. By the time of hospitalization, the patient walked with scissors gait. His older sister (II-2) was 32 years old and had developed progressive weakness of the lower extremities and gait disturbance 20 years ago, accompanied with urinary incontinence for more than 14 years. She had been wheelchair-bound for 4 years by 2014. Notably, their school performances were worse than those of their unaffected siblings and classmates, and this difference showed much

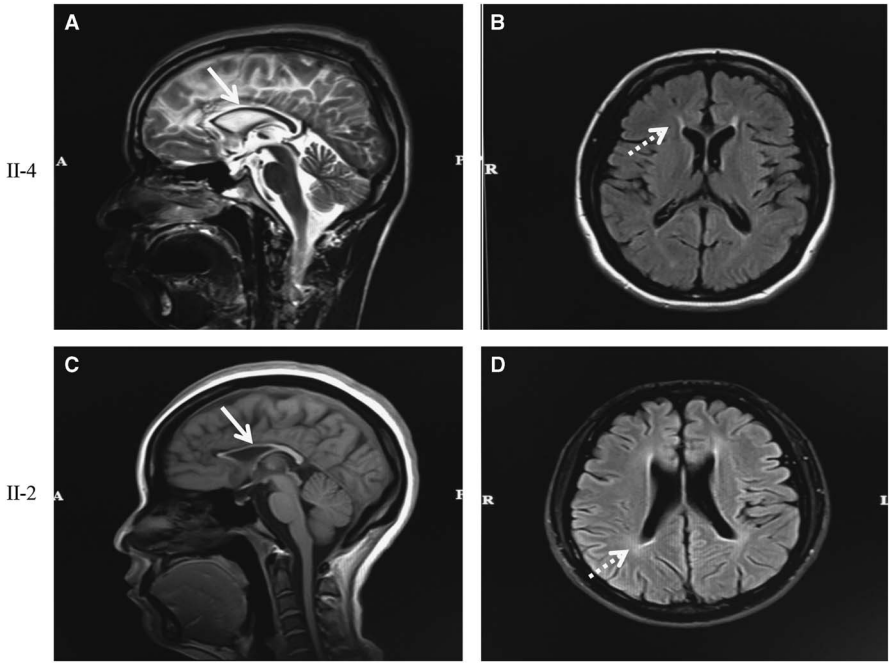

Figure 2: *MRI features of the brain in patients II-4 and II-2. Both patients showed thinning of the corpus callosum on sagittal T2-weighted imaging (A) and sagittal T1-weighted imaging (C) images (arrow). Periventricular leukoaraiosis was found symmetrically in the anterior and posterior horn on fluid-attenuated inversion recovery imaging (B and D, dotted arrow).*

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Table 3: Clinical features of affected individuals in the family

Patient ID	II-4 (Proband)	II-2
Sex	M	F
Age at onset of motor symptoms (yrs.)	25	12
Age at examination (yrs.)	29	32
Age at onset of mental symptoms (yrs.)	Approximately 6	Approximately 6
UL reflexes	++	++
LL reflexes	++++	++++
Ophthalmoplegia	–	–
Decreased vision	–	–
Dysarthria	–	+
Dysphagia	–	–
Cerebellar signs	–	–
Extrapyramidal signs	–	–
Amyotrophy	–	–
Skeletal deformity	Pes cavus	Pes cavus
Urinary incontinence	–	–
WAIS-RC		
VIQ	74	52
PIQ	80	63
FIQ	75	53
EMG/NCV	Normal	Axonal peripheral neuropathy of the upper extremities
MRI (cerebral)		
TCC	+	+
Periventricular leukoaraiosis	+	+
Cortical atrophy	–	–
Ventricular dilation	–	–
Cerebellar atrophy	–	–
MRI (cervical and thoracic spine)	–	–
CSF analysis	–	–

M = male; F = female; UL = upper extremities; LL = lower extremities; WAIS-RC = Wechsler Adult Intelligence Scale-Revised in China; VIQ = Vocable Intelligence Quotient; PIQ = Performance Intelligence Quotient; FIQ = Full Intelligence Quotient; MCV = motor nerve conduction velocity; NCV = nerve conduction velocity; CSF = cerebral spinal fluid; TCC = thin corpus callosum; +, presence; –, absence.

earlier than the motor dysfunction. Unfortunately, because of the parents' poor awareness of mental retardation in their children, they did not noticed their children had poor intelligence performance until they entered a privilege school, which was at approximately 6 years of age. The full-scale IQ scores of patients II-4 and II-2 examined during hospitalization were 75 and 53, respectively. However, no ophthalmoplegia, decreased vision, dysphagia, cerebellar signs, or extrapyramidal symptoms were observed in either patient. There were an additional two siblings (II-1 and II-6) in the parents' generation. The patients' parents (I-1 and I-2) were both 55-year-old farmers. Children III-1 and III-2 of patient II-2 and child III-3 of patient II-4 were both 8 years of age and performed well in school and extracurricular activities including athletics. All seven of these individuals were unaffected and had no complaints of neurological symptoms.

Neurological examination of patients II-4 and II-2 revealed weakness and spasticity of the lower extremities with positive pyramidal signs and pes cavus deformity. Additionally, II-4 exhibited additional upper extremities weakness, whereas II-2 suffered from dysarthria. No sensory impairment or hyperpigmentation of the skin was observed in either patient. Examination of the brain MRI scan revealed that both patients possessed a TCC and periventricular leukoaraiosis (Figure 2). An EMG was performed on each of the patients and revealed the presence of underlying peripheral nerve damage in II-2. Cerebrospinal fluid results were normal for both patients. Detailed information on the two patients is summarized in Table 3. Both patients were classified as having complicated HSP.

Mutation Analysis of the *SPG 11* Gene

Using next-generation targeted sequencing, we found two novel compound heterozygous mutations (c.4001_4002ins ATAAC and c.4057C > G) in the *SPG 11* gene in the proband

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(Figure 3A). Because neither mutation has been previously described, sequencing was extended to validate the identified variants (Figure 3B). Sanger sequencing demonstrated that these compound heterozygous mutations in *SPG 11* were co-segregated with the disease phenotype described by the family pedigree. The detailed results of mutation in this family are illustrated in Figure 1. The affected sister (II-2) also possessed both of these mutations (Figure 4). Individuals who carried either heterozygous

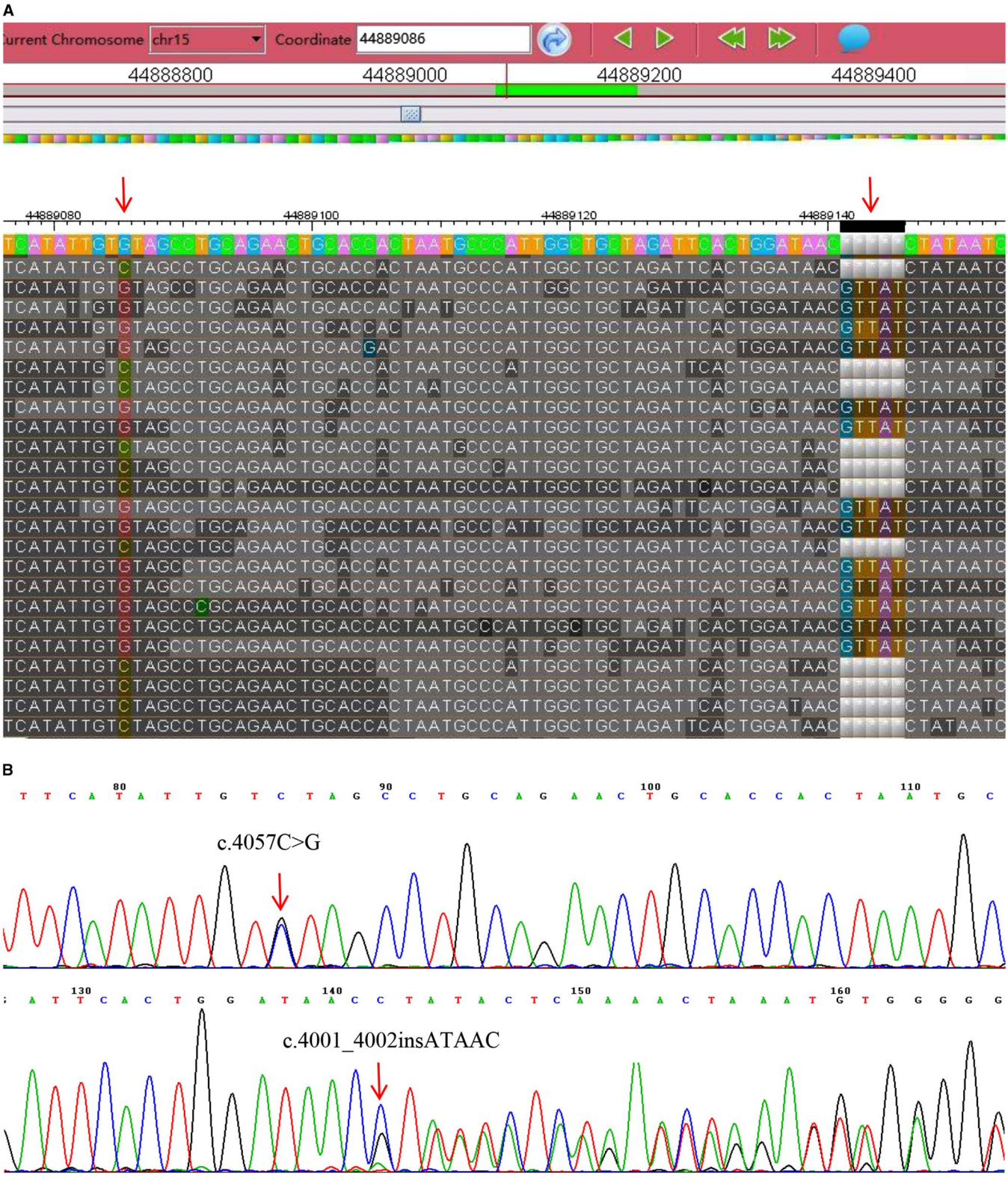

Figure 3: *Identification of the mutations. Variants were detected by targeted exome sequencing (A) and confirmed by Sanger sequencing (B).*

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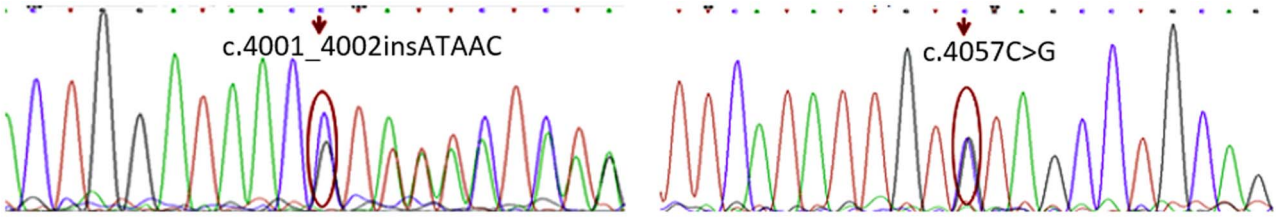

Figure 4: *Sanger sequencing results of the female patient II-2. Sanger sequencing confirmed that II-2 possessed the same mutations as the proband.*

mutation were asymptomatic. The unaffected father (I-1), the son of the proband (III-3), and the son of the female patient (III-1) carried the insertion mutation (c.4001_4002insATAAC) in the heterozygous state. The patients' unaffected mother (I-2), the unaffected youngest sister (II-6), and the daughter of the female patient (III-2) carried the missense heterozygous mutation (c.4057C > G). This mode of inheritance is consistent with an autosomal recessive pattern. The c.4001_4002insATAAC mutation in exon 24 was inherited from the healthy father; this mutation leads to a reading frame shift during transcription, resulting in premature termination of the protein product. The missense mutation c.4057C > G (p.H1353D) was inherited from the unaffected mother; this mutation causes an amino acid substitution from histidine to aspartic acid. It is predicted to be probably damaging by PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) with a score of 0.99 in HumVar (Figure 5), and predicted to affect protein function by SIFT (http://sift.jcvi.org/www/SIFT_enst_submit.html) with a score of 0.00. In addition, conservation analysis of protein revealed that the substituted amino acid is highly conserved among different species (Figure 6); therefore, both mutations are likely to be pathological. Based on the results described here, we propose that these novel compound heterozygous mutations in *SPG 11*, c.4001_4002insATAAC and c.4057C > G, are the genetic cause of ARHSP in this Chinese family.

Discussion

We identified two novel *SPG 11* gene mutations: an insertion mutation (c.4001_4002insATAAC) and a missense mutation (c.4057C > G). These mutations were found in a Chinese ARHSP-TCC pedigree.

To date, 15 distinct loci associated with HSP-TCC have been identified: *SPG 1*, *SPG 11*, *SPG 15*, *SPG 18*, *SPG 21*, *SPG 44*, *SPG*

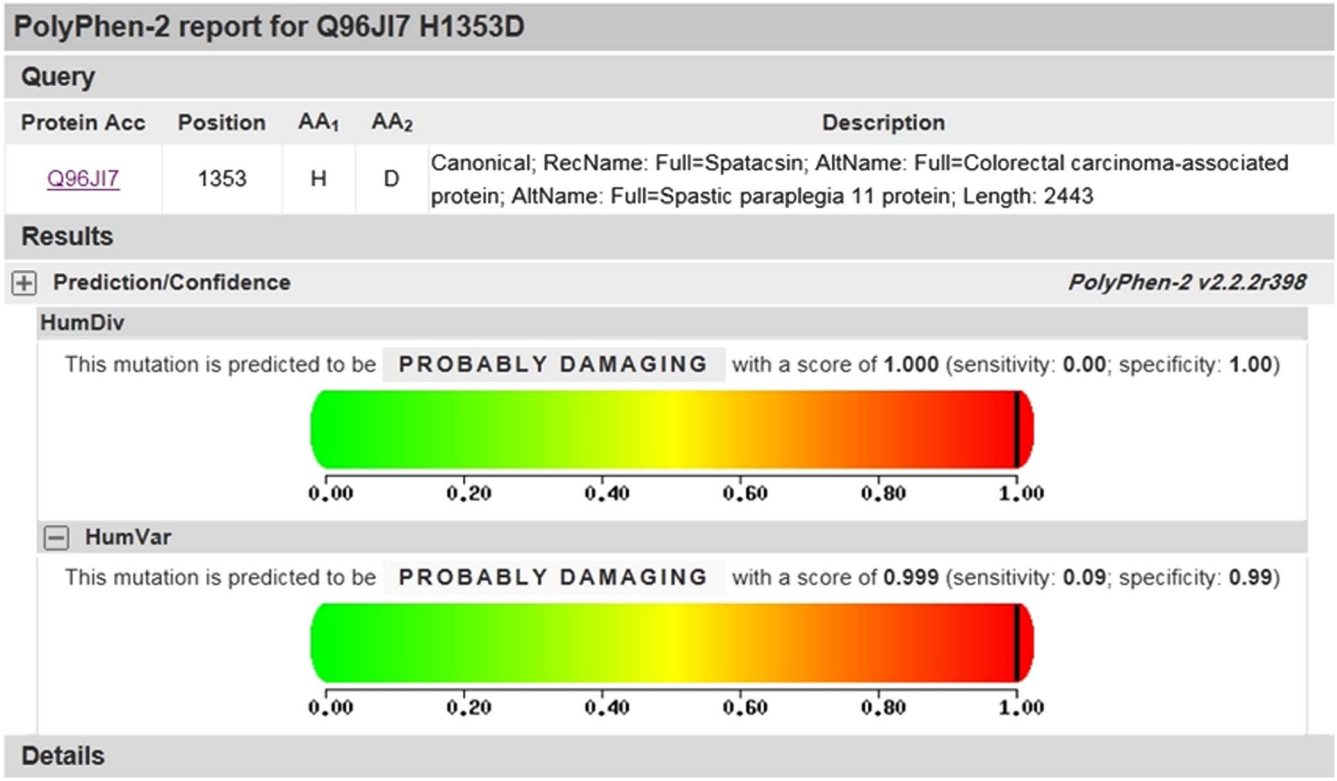

Figure 5: *PolyPhen-2 analysis for c.4057C > G. The mutation of c.4057C > G was predicted to be probably damaging with a score of 1.00 in HumDiv and 0.99 in HumVar.*

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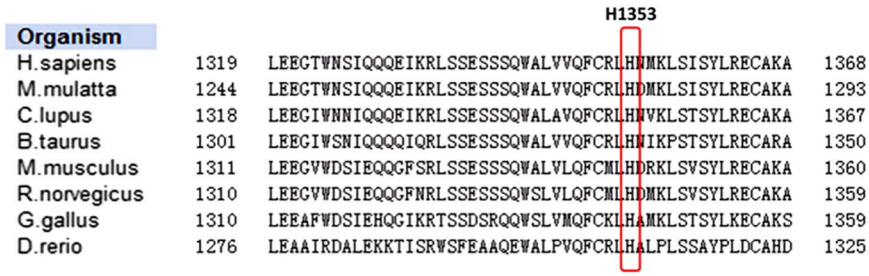

Figure 6: *Conservation analysis. The protein sequence alignment demonstrates that H1353 is highly conserved among all of the species examined.*

45 (65), *SPG 46*, *SPG 47*, *SPG 49*, *SPG 54*, *SPG 56*, *SPG 63*, *SPG 67,* and *SPG 71*.[6,7] It is difficult to determine the disease-causing gene based on the clinical manifestations because a number of coding exons exist in these genes, and traditional screening for each gene is infeasible for clinical applications. We therefore targeted a subset of genes that were potentially responsible for HSP. As a result, we demonstrated that an approach based on exome sequencing of known causative target genes of HSP is an efficient way of identifying pathological genes of interest.

The human *SPG 11* gene, which is located at chromosome 15q13-15, encodes the protein SPATACSIN; this protein is prominently expressed in the cerebellum, cerebral cortex, hippocampus, and pineal gland.[8] It is believed that HSP is a length-dependent distal axonopathy of the corticospinal tracts, resulting in lower limb spasticity and weakness. Several studies are working on alterations in the shaping of organelles, particularly the endoplasmic reticulum, as well as intracellular membrane trafficking and distribution as primary defects underlying the HSP.[9–11] Even so, the protein is still of a lot of unknown characteristics. Among the mutations that have been described in HSP, frame shift, or nonsense mutations are the most frequent types reported in *SPG 11*.[12] Building on this current knowledge base, our study identified two additional mutations, one insertion mutation and one missense mutation, in the *SPG 11* gene. To some extent, these newly identified variants broaden the spectrum of *SPG 11* mutations in Chinese patients and may warrant further investigation in patients.

This family included two affected patients, both of whom presented with weakness and spasticity of the extremities, mental impairment, and a TCC. The disease was absent in the parents and parental consanguinity was not present. Therefore, an autosomal recessive mode of inheritance is almost certainly the case considering that the patients suffered from a compound *SPG 11* genotype. Together, these clinical observations are consistent with the diagnosis of HSP-TCC.[13,14]

ARHSP caused by *SPG 11* mutations is characterized by early-onset progressive spasticity and weakness, a TCC, and cognitive deficits. Approximately 79% of HSP-TCC patients first present with difficulty walking, and only 16% of patients initially present with signs of mental retardation.[15] Our patients showed prominent intellectual disability. This was reflected not only in a low IQ, but also in the onset time of mental retardation, which was earlier than the onset of the abnormal gait. Other clinical manifestations in these patients included spastic paraplegia of the lower limbs, and pes cavus deformity. Patient II-2 also exhibited urinary incontinence, dysarthria and hyperreflexia of the upper limbs. All of these manifestations have been reported in previous studies.

The two patients in the current study did not develop identical symptoms even though they carried the same genetic mutations. In this case, the differences can be interpreted as being as important as the similarities. The female patient started displaying symptoms at age 12, and the disease progressed over the course of 20 years. However, the proband began to develop similar symptoms much later, at the age of 25, and his disease progressed much more quickly. The female patient also showed obvious urinary incontinence, which was notably absent in her brother, who was also a patient. Additionally, the EMG results revealed peripheral neuropathy only in the sister (although no overt symptoms were reported by the patient). We inferred that the peripheral neuropathy was chronic and subclinical. Both patients in this study showed cerebral white matter changes on standard MRI (Figure 2), a finding that was recently reported.[14,16–19] The patients exhibited slight differences in their MRI results; the proband displayed remarkable changes in the anterior region, whereas the sister demonstrated alterations primarily in the posterior aspect. The reason for these differences in the clinical manifestation of the two sibling patients is currently unclear, but it is important to consider several points. First, it is well known that HSP is heterogeneous with regard to its clinical and genetic aspects. Second, the duration of the proband's disease was much shorter than the sister's. The possibility that the proband will develop new symptoms or that the present symptoms will worsen in the future cannot be excluded. Regular follow-up evaluations are scheduled to further describe the evolution of this patient's disease.

In summary, the present results demonstrate that novel compound heterozygous mutations in *SPG 11* are associated with ARHSP in this Chinese pedigree. The results contribute to understanding of the *SPG 11* gene mutation spectrum and highlight the importance of genetic testing in HSP-TCC. Further studies are warranted to investigate the concrete genetic pathogenic mechanisms of HSP-TCC.

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Disclosures

Xiaojie Tian, Min Wang, Kaiyuan Zhang, and Xinqing Zhang do not have anything to disclose.

Statement of Authorship

XT and MW contributed equally to this work.

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