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SPG7 and Impaired Emotional Communication

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Abstract

Objective—The goal of this report is to describe the genetic mutations of a patient with cerebellar degeneration who had ataxia and impaired emotional communication that led to damage of family relationships.

Methods—We extracted genomic DNA from peripheral blood lymphocytes and performed whole-exome sequencing (WES) in this patient and his unaffected parents and siblings. Found mutations were confirmed by Sanger sequencing in each individual.

Results—We found compound heterozygous mutations in the paraplegin (SPG7) gene. One mutated allele has been previously described as a disease-causing missense mutation for spastic paraplegia type 7 (SPG7) (c.1529C>T, p.Ala510Val). The second mutated allele involved a single nucleotide deletion which results in a frameshift in the coding sequence (c.2271delG,

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Author Contributions

Dr. Zhang: Acquisition of data, drafting the manuscript, analysis and interpretation

Dr. McFarland: Study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content

Dr. Subramony: critical revision of the manuscript for important intellectual content, acquisition of data

Dr. Heilman: Acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content

Dr. Ashizawa: Study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, study supervision

Conflict of Interest

This study was sponsored by the Sparkman Fund and NIH grants.

Drs. Zhang and McFarland report no disclosures.

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p.Met757fs*65). The second allele is similar to, but unique from, other described, SPG7-linked truncation mutations.

Conclusions—The abnormal emotional communication in this patient broadens the phenotypic boundary of SPG7.

Keywords

SPG7; emotional disconnection; hereditary spastic paraplegia; cerebellar ataxia

Background

Hereditary spastic paraplegia (HSP) is a neurodegenerative disease characterized by progressive spastic weakness of both legs. While patients with HSP may show an isolated spastic paraparesis, this disease is often associated with additional neurological signs, such as ataxia, mental retardation, epilepsy, peripheral neuropathies, extrapyramidal signs, optic nerve atrophy, and pigmentary retinopathy [1].

The *SPG7* gene maps to chromosome 16q24.3, comprises 17 exons, and encodes the 795 amino acid protein paraplegin. Paraplegin interacts with the ATPase family 3-like 2 (AFG3L2) protein to form the mitochondrial AAA protease complex. Mutations in *SPG7* gene may be a major cause of unexplained ataxia presenting in mid-adult life [2]. Thus, m-AAA protease appears to play critical roles in the maintenance of both cerebellar and corticospinal tract functions.

We report a SPG7 patient with ataxia and mild spasticity who had impaired family relationships that were attributable to an “emotional disconnection.” To remain closely connected with family members it is critical to communicate emotions. Emotions can be communicated by words, and limb gestures; however, two important means of communicating emotions are facial expressions of emotion and emotional prosody (e.g., “It is not what you said, but how you said it.”). This patient was tested for his ability to make emotional facial expressions and to produce emotional prosody with his speech. The means of testing and the results are described in prior paper [3]. In addition to cerebellar dysfunction this patient revealed severe deficits of facial and prosodic emotional communication. We identified compound heterozygous SPG7 mutations in this patient, broadening the clinical spectrum of SPG7 to include the disabling emotional disconnection.

Case report

This college-educated 42-year old man with an 8-year history of slowly progressive, apparently sporadic ataxia developed “emotional disconnection” between him and his family at 39 years of age. At age 42 the total Scale for Assessment and Rating of Ataxia (SARA) score was 8.5 (gait:1.0, stance:2.5, sitting:0, speech:1.0, finger chase:1.0, nose-finger test: 1.0, fast alternating hand movements:1.0, and heel-shin slide:1.0). He showed moderate to severe impairments in expressing emotional prosody and emotional facial expressions as well as frontal executive dysfunctions [3] (Suppl. Table 1). MRI revealed mild to moderate

cerebellar atrophy. Neurological examinations of his parents and siblings were normal (Fig. 1A).

Whole-exome sequencing

Samples were collected under a protocol approved by the University of Florida's Institutional Review Board (IRB) and following informed consent. Genomic DNA from peripheral leucocytes of parents and the proband was subjected to whole exome sequencing (WES) using the Ion Torrent AmpliSeq Exome RDY kit (BGI Tech, Hong Kong) (detail showed in supplementary file). Variant call files were analyzed with Ingenuity Variant Analysis (Qiagen, Redwood City, CA) using an autosomal recessive model. We discovered compound heterozygous mutations in *SPG7* (c.1529 C>T p.Ala510Val and c.2271delG p.Met757fs) in the proband with each parent as heterozygous carriers for one of the mutations (Fig. 1A–C). Sanger sequencing confirmed these results and showed that the proband's siblings (II:3 and II:4) are c.2271delG carriers. The c.1529 C>T p.Ala510Val mutation is the most frequently described mutation in SPG7 [2,4]. The c.2271delG p.Met757fs mutation is a novel mutation (Suppl. Table 2) which replaces final 39 amino acids of the protein with novel 65 amino acids.

Discussion

By WES we identified compound heterozygous mutations of the *SPG7* gene in our patient who developed a late onset, apparently sporadic, cerebellar ataxia with mild spasticity and showed remarkable cognitive impairments. Although cognitive dysfunction has been reported in some SPG7 patients [4], the detailed description is lacking. Our patient has had an extensive neuropsychological evaluation, which revealed frontal executive dysfunctions and affective communication deficits [3]. The affective communication problems were disabling and caused suffering in his family. These neurobehavioral disorders enlarge the clinical spectrum of neurological phenotype of SPG7.

SPG7-HSP is a late-onset (median age 39 years, range 18–52 years) and very slowly progressive disorder that shows a spastic paraparesis, with or without cerebellar dysfunction and cognitive deficits [4]. MRI of the brain frequently shows mild cerebellar atrophy. SPG7 mutations have been found in 18.6% of previously undiagnosed ataxia patients [2]. Most SPG7 patients who were presented with undiagnosed ataxia thus far carried the c.1529 C>T p.Ala510Val mutation in at least one allele (suppl. Table 2). Our patient also carries this mutation and an additional novel frameshift mutation, c.2271delG p.Met757fs, in the *SPG7* gene.

Paraplegin localizes to the inner mitochondrial membrane and forms a complex with Afg3l2. Both paraplegin and Afg3l2 belong to the AAA protein superfamily which act as mitochondrial metalloproteases believed to regulate essential protein quality control [5]. They are highly homologous (40–45% amino acid identity) to two yeast mitochondrial proteins, Yta10p (Afg3p) and Yta12p (Rca1p) [6]. Afg3l2 was more abundant in all tissues examined (5:3 ratio) than paraplegin, and both Afg3l2 and paraplegin were expressed in cerebellar Purkinje neurons, de22712271ep cerebellar nuclei, hippocampal and neocortical pyramidal neurons and motor neurons in brain stem [7]. Mutations in *AFG3L2* have been

reported to cause the autosomal dominant hereditary ataxia SCA28 [8] and the autosomal recessive spastic ataxia-5 (SPAX5) [9]. Since paraplegin is expressed in cerebellar neurons the predominantly ataxic presentation in our SPG7 patient is not surprising. Furthermore, the addition of a novel 65 amino acid sequence at the C-terminal region of the protein resulted from the c.2271delG p.Met757fs mutation (Fig. 1D) may account for the unique phenotypic features described in this patient.

Prefrontal neuronal dysfunction is generally thought to cause impairment of executive functions. We have previously speculated that the cognitive deficits in our patient may be a consequence of cerebellar lesion as the cerebellum has strong projections to the contralateral cerebral cortex and especially the frontal lobes, and therefore a cerebellar lesion could induce frontal-executive cognitive dysfunction and blunting of affect [10]. The mechanism of emotional dysfunction may not only involve the cerebellum connections with frontal lobes but also its connections to portions of the limbic system such as the amygdala [11]. Although limbic dysfunction may have induced this patient's emotional-cognitive dysfunction, the identification of SPG7 mutations in this patient alters this view by introducing a possibility that the SPG7 mutations directly alter the function of relevant cortical neuronal networks since SPG7 is clearly expressed in these cortical neurons. Similar mechanism may also explain intellectual disability that has been observed in patients with AFG3L2 mutations [12].

We conclude that SPG7-HSP is a rare neurodegenerative disease, which may predominantly present with cerebellar ataxia and affective communication deficits in the presence of only mild signs of corticospinal tract dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Fink JK. Hereditary spastic paraplegia: clinico-pathologic features and emerging molecular mechanisms. Acta Neuropathol. 2013; 126:307–28. [PubMed: 23897027]
2. Pfeffer G, Pyle A, Griffin H, Miller J, Wilson V, Turnbull L, et al. SPG7 mutations are a common cause of undiagnosed ataxia. Neurology. 2015; 84:1174–6. [PubMed: 25681447]
3. Heilman KM, Leon SA, Burtis DB, Ashizawa T, Subramony SH. Affective communication deficits associated with cerebellar degeneration. Neurocase. 2014; 20:18–26. [PubMed: 23020242]
4. Klebe S, Depienne C, Gerber S, Challe G, Anheim M, Charles P, et al. Spastic paraplegia gene 7 in patients with spasticity and/or optic neuropathy. Brain. 2012; 135:2980–93. [PubMed: 23065789]
5. Nolden M, Ehses S, Koppen M, Bernacchia A, Rugarli EI, Langer T. The m-AAA protease defective in hereditary spastic paraplegia controls ribosome assembly in mitochondria. Cell. 2005; 123:277–89. [PubMed: 16239145]
6. Bonn F, Pantakani K, Shoukier M, Langer T, Mannan AU. Functional evaluation of paraplegin mutations by a yeast complementation assay. Hum Mutat. 2010; 31:617–21. [PubMed: 20186691]

7. Sacco T, Boda E, Hoxha E, Pizzo R, Cagnoli C, Brusco A, et al. Mouse brain expression patterns of Spg7, Afg3l1, and Afg3l2 transcripts, encoding for the mitochondrial m-AAA protease A. BMC Neurosci. 2010; 11:55. [PubMed: 20426821]

8. Di Bella D, Lazzaro F, Brusco A, Plumari M, Battaglia G, Pastore A, et al. Mutations in the mitochondrial protease gene AFG3L2 cause dominant hereditary ataxia SCA28. Nat Genet. 2010; 42:313–21. [PubMed: 20208537]

9. Pierson TM, Adams D, Bonn F, Martinelli P, Cherukuri PF, Teer JK, et al. Whole-exome sequencing identifies homozygous AFG3L2 mutations in a spastic ataxia-neuropathy syndrome linked to mitochondrial m-AAA proteases. PLoS Genet. 2011; 7:e1002325. [PubMed: 22022284]

10. Krienen FM, Buckner RL. Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. Cereb Cortex. 2009; 19:2485–97. [PubMed: 19592571]

11. Baumann O, Chan E, Mattingley JB. Distinct neural networks underlie encoding of categorical versus coordinate spatial relations during active navigation. Neuroimage. 2012; 60:1630–7. [PubMed: 22300811]

12. Charif M, Roubertie A, Salime S, Mamouni S, Goizet C, Hamel CP, et al. A novel mutation of AFG3L2 might cause dominant optic atrophy in patients with mild intellectual disability. Front Genet. 2015; 6:311. [PubMed: 26539208]

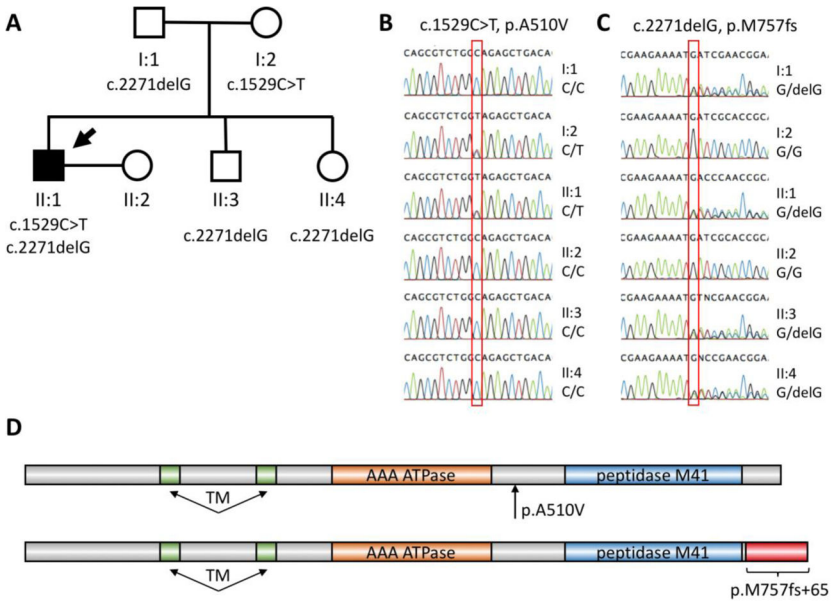

Figure 1. *SPG7* mutations in ataxic patient with impaired emotional communitcation

A) Pedigree and segregation of *SPG7* mutations in this family. Square symbols, male; circle, female; arrow, proband/index patient (II:1). B) Sanger sequencing validation of c.1529C>T, p.A510V *SPG7* mutation. C) Sanger sequence validation of c.2271delG, pM757fs *SPG7* mutation. D) Schematic of mutated SPG7 proteins in proband. Top, p.A510V; bottom, p.M757fs+65; green, transmembrane domain (TM); orange, AAA ATPase domain; blue; peptidase M41 domain; red, novel 65 amino acids from c.2271delG mutation.