

CASE REPORT



## Complicated SPG4 presenting with recurrent urinary tract infection

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### ABSTRACT

We present a 62-year-old woman who developed recurrent urinary tract infections in her early fifties and, after an evaluation by an infectious disease physician, was referred for a neurological consultation. Her history and neurological examination were consistent with spastic paraparesis and there was significant family history of a variety of neurological diagnoses suggesting a genetic disorder. Whole exome genetic testing revealed a novel change, a c.508 C > T variant in the *SPAST* gene. Our genetic and protein modeling analysis suggest that this is a disease-producing mutation confirming the diagnosis of hereditary spastic paraplegia type 4 (SPG4). This patient expands the spectrum of mutations that can cause this disorder and demonstrate the importance of recognizing the role of neurological disorders in causing neurogenic bladder and recurrent urinary tract infections.

### ARTICLE HISTORY

Received 26 March 2020  
Accepted 11 June 2020

### KEYWORDS

Spastic paraplegia type 4; recurrent urinary tract infection; neurological disorders; *SPAST* gene

## 1. Introduction

Spastic paraplegia (SPG) refers a group of neurodegenerative disorders characterized by progressive weakness and spasticity of the limbs that may be inherited in an autosomal dominant or recessive fashion. An autosomal dominant form (SPG4), spastic paraplegia type 4, accounts for about 45% of all SPG and is caused by mutations in the *SPAST* gene which encodes spastin, an ATPase protein belonging to the ATPase family associated with various cellular activities (AAA) [1]. SPG4 can occur in an uncomplicated form where clinical features include only spasticity of the limbs. In contrast, complicated forms can present with additional neurological features that can include dementia, cerebellar ataxia, or epilepsy. The *SPAST* gene penetrance, severity, and age of onset are variable but most individuals first experience symptoms in early childhood [2]. We present genotype–phenotype analysis of a patient with complicated SPG4.

## 2. Case presentation

This is a 62-year-old woman who presented with progressive weakness and gait abnormalities which began in her early fifties. As the symptoms progressed, she developed frequent urinary tract infections and was referred to an infectious disease physician. The multiple urinary infections prompted the infectious disease doctor to recommend a neurological consultation.

Her neurological examination revealed a normal mental status and cranial nerve examination. Tests of her sensation and cerebellar system disclosed no

abnormalities. Her stretch reflexes were symmetrical and 4+ at the ankles with sustained clonus, 3+ at the patellae with crossed adductor responses. Her extensor responses were plantar. In her arms, testing the brachioradialis, biceps, and triceps reflexes showed normoactive responses (2+). The muscle tone was increased in her legs and she had a spastic gait with scissoring. Her muscle bulk was normal and she had normal power except for mild weakness of hip flexion bilaterally (Medical Research Council Grade 4/5). Prior investigations that had been performed and the following were negative or normal: MRI of the brain, cervical, and thoracic spine with and with contrast, routine serum chemistries and cell blood counts, and an electromyogram which showed no evidence of neuropathy, myopathy, or motor neuron disease.

A family history revealed many individuals affected with a neurological disorder including a brother with ‘neuropathy’ and father with ‘amyotrophic lateral sclerosis’. She also has a paternal uncle and a male cousin diagnosed with difficulty walking due to a neurological disorder. The presence of these multiple members of her family diagnosed with a neurological disorder suggests a genetic disorder with an autosomal dominant pattern of inheritance. Her neurological examination was highly suspicious for SPG and genetic testing was performed focusing on genes that cause this disorder.

The patient underwent Whole Exome Sequencing (WES) through a commercial company. No variants were reported in any gene except for a c.508 C > T variant in the *SPAST* gene. This variant was further investigated

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by interrogating publicly available databases and our internal database. Our internal database is a collection of gene variants with a frequency of less than 3% generated from whole-exome sequencing data of 72 patient samples with neurological disorders. The c.508 C > T variant is novel and has been deposited in ClinVar database, rs886039695, without any associated phenotypic data. It has not been reported in any other public databases (1000 G, ExAC, NHLBI) or our internal database. It is predicted to be disease causing by the protein modeling program, mutation Taster [3]. The c.508 C > T variant results in p.Q170X, a stop gain mutation and causes protein truncation or non-sense mediated mRNA decay resulting in loss of normal protein function. Our protein modeling analysis combined with the phenotype of the patient that is consistent with SPG provides strong evidence that this variant is pathogenic.

### 3. Discussion

SPG caused by mutations in the *SPAST* gene is typically inherited in an autosomal dominant manner and most commonly cause an uncomplicated form of spastic paraplegia. The ClinVar database reports 99 pathogenic SPG causing variants and an additional 21 variants with unknown significance in *the SPAST* gene. The encoded protein, spastin is associated with microtubule cytoskeleton and promotes microtubule disassembly [4]. The variant in our patient, c.508 C > T, p.Q170X, occurs in exon 2 which affects the microtubule interacting and trafficking domain (116–197 aa) where 7.2% of disease-causing *SPAST* mutations have been reported. A nearby variant, c.499 C > T, p.Gln167X causing pure HSP has been previously reported in one family [5].

Interestingly in this patient, the original referral to the neurologist was made by the infectious disease specialist based on an evaluation of recurrent bladder infections. Bladder involvement can represent a significant source of morbidity in SPG [6,7]. Our patient suffers from a neurogenic bladder resulting in abnormal bladder storage and emptying. The mechanisms leading to neurogenic bladder are complex and normal functioning requires coordination between the peripheral and central nervous systems. The clinical manifestations of neurogenic bladder in SPG include incontinence, hesitancy, frequency, and urgency often occurring simultaneously [7]. In addition, there remains significant morbidity and mortality associated with neurogenic bladder from infections leading to sepsis [8].

Our case demonstrates the importance of recognizing the role of neurological disorders such as SPG causing neurogenic bladder and susceptibility to recurrent bladder infections. It also expands the spectrum of mutations in the *SPAST* gene that can cause complicated SPG.

### Author's contributions

All authors contributed to the initial draft of this manuscript; LRP and KO revised the later drafts. All authors reviewed and approved the final draft.

### Disclosure statement

The authors report no conflict of interest.


### Funding

The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

### Ethics and consent

The study was conducted following policies and procedures approved by the local Institutional Review Board. Informed consent was obtained from the individuals who participated in this study.

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