

# Clinical/Scientific Notes

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## SPG7 MUTATIONS ARE A COMMON CAUSE OF UNDIAGNOSED ATAXIA

**OPEN**

Late-onset ataxias are clinically and etiologically diverse. Patients rarely have defining clinical features, and many remain classified as idiopathic, despite extensive clinical, metabolic, and genetic investigations. Here we show that mutations in a gene known to cause hereditary spastic paraplegia (*SPG7*) are a major cause of unexplained ataxia presenting in mid-adult life.

**Methods.** Exome sequencing in 2 undiagnosed ataxia patients identified compound heterozygous *SPG7* mutations, not previously considered likely in the absence of pyramidal signs. This prompted us to prospectively study *SPG7* in 70 other probands with undiagnosed ataxia and pyramidal signs attending routine follow-up over a 12-month period. Other sporadic and inherited causes of ataxia were excluded, including inflammatory, metabolic, neoplastic, and sporadic degenerative ataxia; spinocerebellar ataxia 1, 2, 3, 6, 7, 10, 12, and 17; dentatorubral-pallidoluysian atrophy; and Friedreich ataxia. Mutations in *SPG7* were detected by Sanger sequencing of all 17 coding exons and multiplex ligation-dependent probe amplification analysis (MRC-Holland kit P213-B1, Amsterdam, the Netherlands). All patients provided written informed consent.

**Results.** Exome sequencing identified 2 *SPG7* mutations in patient 1 (c.1529C>T/p.Ala510Val and c.1715C>T/p.Ala572Val) and 2 in patient 3 (c.1529C>T/p.Ala510Val and c.1192C>T/p.Arg398\*). These were confirmed by Sanger sequencing, and present in their affected siblings (patients 2 and P4, respectively). The variants were heterozygous in the unaffected parents, and were previously reported as pathogenic.<sup>1</sup> No other recessive mutations in relevant disease genes were identified (tables e-1 to e-4 on the *Neurology*<sup>®</sup> Web site at Neurology.org).

Of the 70 patients subsequently studied, 13 had likely recessive mutations (4 homozygous and 9 compound heterozygous). Two patients had novel mutations (c.1225\_1229del/p.Glu409Arg\_fs49\* and

c.2228T>C/p.Ile743Thr). All patients had the c.1529C>T/p.Ala510Val mutation on at least one allele. All patients were of British descent. No rearrangements were detected. The clinical features are summarized in table 1.

At initial presentation, all the patients presented with symptoms of ataxia or gait disturbance (mean age 36.3 years, SD 12.5). Midline ataxia was present in all patients at onset, with gait ataxia present in all patients and ocular signs in 5. Eleven patients (65%) had no pyramidal signs (normal reflexes, and no spasticity). Ocular findings were present in 5 (29%) patients.

On follow-up examination, most patients (76%) developed appendicular ataxia. All developed clear pyramidal signs: 12 had overt spasticity, and the remainder developed brisk tendon reflexes or extensor plantar responses. Ocular findings were present in 11 (65%), with nystagmus being the most common finding and partial ophthalmoparesis or slow saccades in 7 (41%). Twelve patients had brain MRI, with 11 (93%) showing cerebellar atrophy. Cervical spine MRI (n = 5) was normal in 4, with 1 patient having a likely incidental thoracic syrinx. Muscle biopsy identified cytochrome *c* oxidase–negative fibers in 2 patients, multiple mtDNA deletions in 1 patient, and coenzyme Q10 deficiency in a single patient.

**Discussion.** We were surprised to find likely pathogenic *SPG7* mutations in 18.6% of patients with unexplained ataxia. Although these patients did not have pure ataxia on follow-up, it was the predominating feature, and the patients had been clinically diagnosed and investigated for ataxic disorders. In our *SPG7* patients, even after an average follow-up of 16.8 years, the pyramidal signs were subtle in many, endorsing our conclusion that a gene identified in patients with autosomal recessive hereditary spastic paraplegia should be considered in adults with unexplained ataxia. Eight (57%) of the probands had no relevant family history, so *SPG7* should even be considered in sporadic cases. Combining these findings with another novel clinical presentation of *SPG7*,<sup>2</sup> we provide the first minimum prevalence of *SPG7*-related disease at 0.72/100,000, making this a common cause of inherited ataxia, comparable with both autosomal

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Supplemental data  
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**Table 1** Clinical features and molecular findings in 17 patients with SPG7 mutations

Patient no.	Mutation 1	Mutation 2	First symptom	Onset age, y	FHx				
1	c.1529C>T, p.Ala510Val	c.1715C>T, p.(Ala572Val)	Ataxia	35	Patient 2				
2	c.1529C>T, p.Ala510Val	c.1715C>T, p.(Ala572Val)	Ataxia	35	Patient 1				
3	c.1529C>T, p.Ala510Val	c.1192C>T, p.Arg398*	Ataxia	25	Patient 4				
4	c.1529C>T, p.Ala510Val	c.1192C>T, p.Arg398*	Ataxia	28	Patient 3				
5	c.1529C>T, p.Ala510Val	c.233T>A, p.(Leu78*)	Gait imbalance	33					
6	c.1529C>T, p.Ala510Val	c.1715C>T, p.(Ala572Val)	Clumsy hands	32	Sibling				
7	c.1529C>T, p.Ala510Val	c.1715C>T, p.(Ala572Val)	Gait imbalance	45	Sibling				
8	c.1529C>T, p.Ala510Val	c.1529C>T, p.Ala510Val	Clumsy	Teens					
9	c.1529C>T, p.Ala510Val	c.2228T>C, p.(Ile743Thr)	Gait imbalance, dysarthria	29					
10	c.1529C>T, p.Ala510Val	c.1529C>T, p.Ala510Val	Clumsy	10					
11	c.1529C>T, p.Ala510Val	c.1053dup, p.(Gly352Argfs*44)	Gait imbalance	49					
12	c.1529C>T, p.Ala510Val	c.1225_1229del, p.(Glu409Argfs*49)	Gait imbalance	54	Sibling				
13	c.1529C>T, p.Ala510Val	c.1529C>T, p.Ala510Val	Gait imbalance	46					
14	c.1529C>T, p.Ala510Val	c.1529C>T, p.Ala510Val	Gait imbalance, dysarthria	46					
15	c.1529C>T, p.Ala510Val	c.1715C>T, p.(Ala572Val)	Dysarthria	18					
16	c.1529C>T, p.Ala510Val	c.1053dup, p.(Gly352Argfs*44)	Gait imbalance	Childhood	Sibling				
17	c.1529C>T, p.Ala510Val	c.1053dup, p.(Gly352Argfs*44)	Balance	40	Sibling				
<b>Signs at presentation</b>									
Patient no.	Ataxia	Weakness	Hyperreflexia	EPR	Spasticity	Cerebellar dysarthria	Ocular	Bladder	
1	L/G		3+			+	Nystagmus		
2	L/G								
3	G		3+		Mild	+			
4	G		3+		Mild	+			
5	G		3+	+	LE				
6	L/G								
7	G		3+				Sac		
8	G						Nystagmus		
9	G								
10	L/G							Fr	
11	G								
12	L/G	4+	3+						
13	G								
14	G					+	Sac		
15	G					+			
16	G								
17	G					+	Dip		
<b>Signs at last follow-up</b>									
Patient no.	Interval, y	Ataxia	Weakness	Hyperreflexia	EPR	Spasticity	Cerebellar dysarthria	Ocular	Bladder
1	9	L/G		3+	+	LE	+	Nystagmus	U/I
2	13	L/G		4+		LE	+	Nystagmus	
3	23	G		3+		LE	+		
4	18	G		3+		LE	+		
5	12	L/G		4+	+	UE/LE	+	PEO, nystagmus	
6	15	L/G		4+	+	LE	+	PEO	U

Continued

**Table 1** Continued

Patient no.	Interval, y	Signs at last follow-up							
		Ataxia	Weakness	Hyperreflexia	EPR	Spasticity	Cerebellar dysarthria	Ocular	Bladder
7	5	L/G		3+		LE		Sac	
8	20	L/G		3+			+	Nystagmus	
9	5	G		4+	+	LE	+		
10	27	L/G		3+	+	LE	+	PEO, Sac, OA	
11	3	L/G		4+		UE/LE	+		
12	50	L/G	4+	3+	+	LE		PEO	
13	8	G		3+	+	LE	+	Sac	DI
14	3	G>>L		3+	±		+	Nystagmus	
15	25	L/G		3+		UE/LE	+		
16	35	L/G		3+	+	LE			Fr
17	23	L/G		2+	+		+	PEO, nystagmus	

Abbreviations: DI = detrusor instability; EPR = extensor plantar response; FHx = family history; Fr = frequency; G = gait; I = incontinence; L = limb; LE = lower extremity; OA = optic atrophy; PEO = ophthalmoparesis; Sac = slow saccades; U = urgency; UE = upper extremity.

dominant spinocerebellar ataxia (1.59/100,000)<sup>3</sup> and Friedrich ataxia (1.8/100,000).<sup>4</sup> This is probably an underestimate given the late presentation of some cases. All of our patients had p.Ala510Val, reaffirming the pathogenicity of this allele, which has been considered a low frequency polymorphism (0.3463% in EVS, dbSNP rs61755320). This study illustrates the advantage of exome sequencing in neurogenetic disorders, where genes initially shown to cause one classical phenotype (such as hereditary spastic paraplegia) can also cause other phenotypes in a subgroup of patients (such as ataxia).

*SPG7* encodes paraplegin, which is a component of the mitochondrial AAA protease, and the binding partner of AFG3L2.<sup>5</sup> Both paraplegin and AFG3L2 are highly expressed in Purkinje neurons,<sup>6</sup> and mutations in *AFG3L2* cause spinocerebellar ataxia type 28.<sup>7</sup> This explains why the phenotypic spectrum of *SPG7* includes a predominantly ataxic presentation. It will be interesting to see whether specific mutations predispose to an ataxic or spastic presentation when cohorts increase in size. However, given the diverse nature of the clinical presentations, a more inclusive disease name such as parapleginopathy may avoid the misleading expectation that spasticity always predominates in this condition. Future study should address the relative likelihoods of these various presentations along the phenotypic spectrum of paraplegin-related diseases.

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### ANTI-MOG ANTIBODIES WITH LONGITUDINALLY EXTENSIVE TRANSVERSE MYELITIS PRECEDED BY CLIPPERS

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is an inflammatory brainstem syndrome of uncertain etiology, with distinct radiologic features.<sup>1</sup> Autoimmunity has been postulated, although specific CNS antibodies have not been reported. Our patient initially presented with classical clinicoradiologic features of CLIPPERS. Five months later, she developed a longitudinally extensive spinal cord inflammatory lesion affecting mainly the conus, and had antibodies to myelin-oligodendrocyte glycoprotein (MOG). Although neuromyelitis optica spectrum disorders (NMOSD) with brainstem involvement may feature in the broad differential diagnosis of CLIPPERS, this is the first report describing an overlap with the anti-MOG phenotype of NMOSD, and highlights that CLIPPERS may not be a distinct nosologic entity.

**Case report.** A 36-year-old woman presented with a 2-week history of dizziness, left facial paresthesia, allodynia, and altered intraoral sensation. Shortly before admission, she developed slurred speech, gait ataxia, and double vision. There were no constitutional symptoms suggesting systemic illness.

Examination revealed diplopia, horizontal nystagmus on left gaze, dysarthria, and left-sided facial weakness. Visual acuities and fundal appearances were normal, as were tone, power, sensation, and sphincter function. Limb reflexes were brisk, without clonus. Her gait was ataxic.

Brain MRI showed patchy pontocerebellar signal change (figure, A–D), consistent with CLIPPERS.<sup>1</sup> CT of the chest/abdomen/pelvis was normal. CSF showed 2 lymphocytes/ $\mu$ L and elevated protein (686 mg/L). Microscopy, culture, and viral PCR were negative. Flow cytometry identified reactive T cells (CD4:CD8 ratio 3:1). CSF oligoclonal bands were negative. Angiotensin converting enzyme levels were normal, and antinuclear antibody screening was negative.

As symptoms were progressing, we commenced treatment with high-dose steroids (3 days IV methylprednisolone; thereafter 1 mg/kg/day prednisolone). Subsequently, the clinical findings and imaging appearances improved markedly (figure, E).

With full symptom resolution, steroids were slowly weaned and discontinued 5 months after initial admission. Two weeks later, the patient developed progressive painful tightness in both legs, altered perineal sensation, difficulty climbing stairs, and transient urinary retention requiring catheterization. She had a spastic paraparesis, pyramidal weakness, brisk 4-limb reflexes, crossed adductor jerks, and bilateral patellar and ankle clonus. Left leg pinprick and temperature sensation were reduced. Upper limb, cranial nerve, and cerebellar examination results were normal.

MRI showed residual pontine changes and a new long cord lesion involving the conus (figure, F).

CSF studies revealed 18 lymphocytes, elevated protein (554 mg/L), and again a reactive picture without clonality on flow cytometry. Oligoclonal bands remained negative.

Aquaporin-4 (AQP4) antibodies were negative, but serum anti-MOG immunoglobulin G1 antibodies were positive using a cell-based assay using full-length human MOG.

Our patient received further pulsed and maintenance steroids. One month later, her myelopathic symptoms had fully resolved.

**Discussion.** The initial presentation of a steroid-responsive brainstem encephalitis with curvilinear and nodular pontocerebellar enhancement and T-cell-predominant CSF leukocytosis suggested CLIPPERS syndrome.<sup>1</sup>

Alternative diagnoses included autoimmune or parainfectious disorders, neoplasia (particularly primary CNS lymphoma), vasculitis, and infection. Central pontine myelinolysis can occasionally enhance, but there were no precipitating factors, and the lesion appearances are atypical. Behçet or sarcoidosis can cause multifocal lesions, but there were no systemic features raising suspicion of these (e.g., orogenital ulceration, uveitis, skin, joint, or respiratory involvement). Paraneoplastic antibodies were not screened; however, the subsequent clinical course was not suggestive of a paraneoplastic etiology. Given unequivocal and rapid improvement with steroids, brainstem biopsy to exclude malignancy was believed to be of unacceptably high risk.

Although often monophasic, CLIPPERS can relapse after discontinuation of immunotherapy and