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Mutation of *SELENOI* and *LAMA1* Causes Hereditary Spastic Paraplegia

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Introduction

Hereditary Spastic Paraplegia (HSP) is a rare neurodegenerative disorder characterized by weakness and spasticity in the lower limbs. HSP primarily affects the muscle function in the lower limbs, making everyday movements challenging. It is caused by genetic factors, with various gene mutations contributing to its development. HSP has various forms and often follows an autosomal dominant inheritance pattern. Treatment focuses on symptom management and relief, including physical therapy and the use of assistive devices. While there is no cure, appropriate management strategies can improve patients' quality of life. Additionally, genetic counseling is important for assessing familial risk and preparing necessary precautions. The SELENOI and LAMA1 genes play essential roles in regulating cellular functions, both internally and externally. The SELENOI gene is associated with neuronal function and primarily operates within the cell, regulating intracellular signaling pathways and influencing cell cycle and motor impairment. The LAMA1 gene, on the other hand, controls the formation and structure of the extracellular matrix, impacting neuronal growth and stability. While mutations in these genes are associated with various neurological disorders, there is no direct evidence linking to HSP.

Case report

We report a 19-year-old male diagnosed with HSP. The patient was born at 40 weeks of gestation and showed lower limb weakness and developmental delay one year after birth, undergoing outpatient rehabilitation therapy regularly since then. Despite interventions such as botulinum toxin injection and tenotomy surgery for lower limb spasticity, his condition persisted. Manual muscle testing revealed overall poor grade in the lower limbs, and spasticity was graded as 2 on the Modified Ashworth Scale (Table 2). The modified Barthel Score (MBI) and Functional Independence Measure (FIM) to measure the level of independence in activities of daily living. Berg Balance Scale (BBS), a clinical test of a person's static and dynamic balance abilities, was also administered. The results of these assessments, as presented in Table 3, indicated notable deficiencies in ambulation and a lack of dynamic balance. Next-generation sequencing (NGS) revealed a homozygous variant in the SELENOI gene (NM_033505.4:c.797C>T:p.(Pro266Leu)) and a heterozygous variant in the LAMA1 gene (NM_005559.4:c.4579C>T:p.(Gln1527Ter)) (Table 1). The patient has a 24-year-old female sibling diagnosed with HSP. To confirm genetic association, NGS was performed on her as well, revealing a heterozygous variant in the SELENOI gene and a homozygous variant in the LAMA1 gene. Brain image of the patient and the sibling show diffuse cerebral and cerebellar atrophy (Figure 1).

Table 1. Next-generation sequencing (NGS) result of the patient and the sibling

The Patient NGS

Gene	Accession	Nucleotide	Amino acid	Zygosity	dbSNP	Inheritance
SELENOI	NM_033505.4	c.797C>T	p.Pro266Leu	Homo		AR
LAMA1	NM_005559.4	c.4579C>T	p.Gln1527Ter	Hetero	rs746183130	AR

The Sibling NGS

Gene	Accession	Nucleotide	Amino acid	Zygosity	dbSNP	Inheritance
SELENOI	NM_033505.4	c.797C>T	p.Pro266Leu	Hetero		AR
LAMA1	NM_005559.4	c.4579C>T	p.Gln1527Ter	Homo	rs746183130	AR

Table 2. Modified Ashworth Scale

	Right	Left
Shoulder flexor	G0	G0
Shoulder extensor	G0	G0
Elbow flexor	G0	G0
Elbow extensor	G0	G0
Hip flexor	G1+	G1+
Hip extensor	G1+	G1+
Knee flexor	G1+	G1+
Knee extensor	G1+	G1+
Ankle dorsi flexor	G0	G0
Ankle plantar flexor	G1	G1

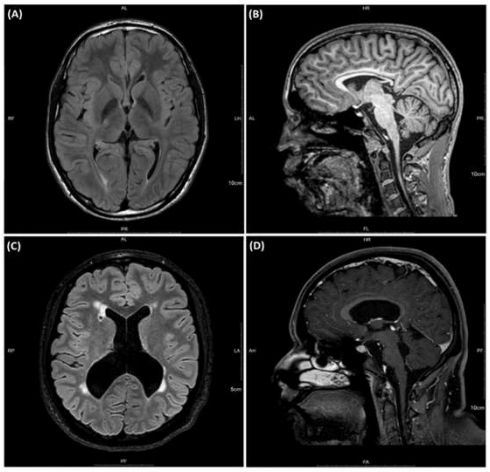

Figure 1. Brain MRI of the patient [T2-weighted axial view (A), T1-weighted sagittal view (B)] shows diffuse cerebral and cerebellar atrophy, with thinning of the corpus callosum. Brain MRI of the sibling [T2-weighted axial view (C), T1-weighted sagittal view (D)] shows diffuse cerebral and cerebellar atrophy, with ventriculomegaly.

Table 3. Modified Barthel Index (MBI), Functional Independence Measure (FIM), and Berg Balance Scale (BBS)

MBI		
Personal hygiene		5
Bathing self		3
Feeding		10
Toilet		10
Stair climbing		5
Dressing		8
Bowel control		10
Bladder control		10
Ambulation		8
Chair/bed transfer		15
Total		84

FIM		
Self-care	Eating	7
	Grooming	7
	Bathing	4
	Dressing-Upper	7
	Dressing-Lower	6
	Toileting	6
Sphincter Control	Bladder	7
	Bowel	7
Transfers	Bed, Chair, W/C	6
	Toilet	6
	Tub, Shower	6
Locomotion	Walk, Wheelchair	1
	Stairs	1
Comprehension	Comprehension	7
	Expression	7
Social Cognition	Social Interaction	7
	Problem Solving	4
	Memory	7
Total		101

BBS	
Sitting to standing	2
Standing unsupported	2
Sitting unsupported	4
Standing to sitting	1
Transfers	3
Standing with eyes closed	2
Standing with feet together	0
Reaching forward with outstretched arm	1
Retrieving object from floor	0
Turning to look behind	1
Turning 360 degrees	0
Placing alternate foot on stool	0
Standing with one foot in front	0
Standing on one foot	0
Total	16

Conclusion

This case report presents a patient with mutations in the SELNOI and LAMA1 genes, exhibiting typical HSP symptoms. Genetic analysis confirmed mutations in these genes, contributing to a better understanding of the mechanisms behind HSP onset related to SELENOI and LAMA1. Tailored treatment approaches accounting for these genetic mutations are essential for effectively managing the patient. Hence, this study offers significant insights into genetic mechanisms and management of HSP.