Hereditary Spastic Paraplegia due to *LYST* Gene Mutation: A Novel Causative Gene

Dear Sir,

Hereditary spastic paraplegias (HSP) are a diverse group of inherited neurodegenerative disorders characterized by insidiously progressive spasticity of the lower extremities as their core defining clinical features.[1,2] The designation Spastic paraplegia gene (SPG) has been given to 83 clinical–genetic forms of HSP. However, there are more than 25 genes causing HSP that not been assigned an SPG designation ("non-SPG" genes). The lysosomal trafficking regulator (*LYST)* gene is one of the non-SPG genes that has been reported to cause complicated HSP.[3] Hereby, we report a 50-year-old male patient who presented with progressive lower limb spasticity with an exaggerated deep tendon reflex. Whole-exome sequencing showed a missense mutation in the *LYST* gene, which has not been reported in India.

A 50-year-old man born out of consanguineous parentage presented with progressive difficulty walking for a 2-year duration. The walking difficulty was due to stiffness in both lower limbs. He had urinary urgency with occasional incontinence for 1 year. There was no diurnal variation, stiffness in upper limbs, wasting of limbs, craniobulbar symptoms, sensory symptoms, incoordination, seizures, or cognitive decline. There were no similar complaints from his siblings or parents [Figure 1]. The systemic examination was unremarkable. Neurological examination showed normal cognition, speech, and cranial nerves. Motor examination showed lower limb power of 5/5 and upper limb power of 5/5, spasticity in both lower limbs (grade 3 according to the modified Ashworth scale), grade 4+ deep tendon reflexes in the lower limbs, and grade 3+ in the upper limbs and an absent jaw jerk. Sensory examination was normal. There were no signs of incoordination, and Romberg's test was negative. Plantar responses were extensor. A clinical diagnosis of spastic paraplegia probably hereditary was considered. Complete hemogram, renal, hepatic, and thyroid functions were normal. Serological tests for human immunodeficiency virus and syphilis were negative. The serum paraneoplastic antibodies and vasculitis panel were negative. Serum vitamin B12, homocysteine, and lactate were normal. The whole spine and brain magnetic resonance imaging was normal with no corpus callosal abnormalities or "ear of the lynx" sign. The cerebrospinal fluid analysis was normal. Somatosensory evoked potentials of the median nerve and tibial nerves showed normal cortical potentials. Nerve conduction studies were normal. Whole-exome sequencing showed homozygous missense variant NM_000081.4(LYST):c. 28C>A (p.Arg10Ser) at exon 3 in the *LYST* gene. This variant has not been reported previously as a benign variant. The p.Arg10Ser variant is novel (not in any individuals) in 1 kG, gnomAD, and in our in-house database. The gene *LYST* has a low rate of benign missense variation as indicated by a high missense variant Z-score of 1.41. The p. Arg10Ser missense variant is predicted to be damaging by both Sorting Intolerant From Tolerant (SIFT) and Polymorphism Phenotyping v2 (PolyPhen2). The phenotype of the proband matches that of the disorder caused by pathogenic variants in the *LYST* gene. For these reasons, this variant was classified as likely pathogenic. After ruling out etiologies for compressive and non-compressive myelopathy, a final diagnosis of pure HSP was made due to the *LYST* gene mutation. The patient was started on oral baclofen for spasticity and darifenacin for spastic bladder symptoms. He had mild symptomatic improvement in the spasticity of the lower limbs at a 3-month follow-up.

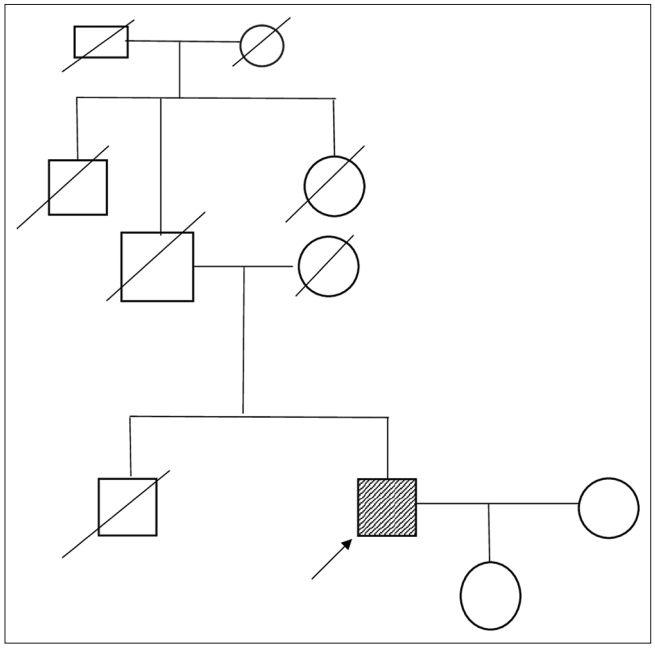

Figure 1: Pedigree of the proband

HSP can be clinically classified as a pure and complicated HSP. Pure HSP is characterized by spasticity of both lower limbs with brisk tendon reflexes and posterior column dysfunction, whereas complicated HSP has in addition cerebellar ataxia, dementia, peripheral neuropathy, amyotrophy, extrapyramidal symptoms, optic atrophy, and deafness.[4] HSP remains a diagnosis of exclusion in sporadic cases. An autosomal-dominant (AD), autosomal-recessive (AR), or X-linked recessive (XR) pattern of inheritance is seen in HSP. Pure HSP is more commonly inherited in the AD pattern, and SPG4 is the most common AD-HSP constituting 50% of cases.[5] HSPs presenting as pure HSP are SPG12, SPG13, SPG19, SPG41, and SPG42 with AD inheritance, SPG24, SPG62, and SPG83 with AR inheritance, and SPG34 with XR inheritance.[1] One of the various underlying pathomechanisms includes disruption of intracellular trafficking due to impaired axonal transport of molecules and organelles affecting the distal parts of motor neurons.[6] The gene *LYST* is

known as the causative gene for Chédiak–Higashi syndrome (CHS, OMIM #214500). CHS is characterized by severe immune deficiency, frequent bacterial infections, hypopigmentation, a bleeding tendency, and neurological dysfunction.[7] In adults with CHS, neurological dysfunction predominates in the absence of immune deficiency and bleeding tendency. The neurological dysfunction includes cerebellar ataxia, neuropathy, parkinsonism, dementia, and spastic paraplegia.[8,9]

The *LYST* gene is a large gene with 51 coding exons and an open reading frame of 11 403 kb. The LYST protein is a cytoplasmic protein involved in the control of the exocytosis of secretory lysosomes. The protein also acts as a scaffold protein mediating the fusion or fission event of vesicles. Karim *et al*.[9] (2002) first reported adult cases with *LYST* gene missense mutations (R1563H or V1999D) who had spastic paraplegia with nystagmus. Later, Shimazaki *et al*.[3] (2014) reported two patients in a Japanese family with a homozygous missense mutation (c. 4189T>G, p.F1397V) in the *LYST* gene. Both patients had an age of onset of symptoms in the fifth decade with bilateral lower limb spasticity, brisk reflexes, gait ataxia, sensory neuropathy, and reduced Mini-Mental State Examination score. A peripheral blood smear examination showed large granules in the proband's leukocytes and large peroxidase-positive ones in granulocytes. The mutation (p. F1397V) was located within the ConA-like lectin domain of the LYST protein. Our patient presented with a phenotype suggestive of pure HSP with an age at onset of 48 years without family history. We found a missense mutation (p.R10S) in the *LYST* gene.

Pure HSP is more commonly inherited in the AD pattern, and the genes causing pure HSP are limited. Mutation in the *LYST* gene (non-SPG gene) is one of the causes of isolated adult-onset pure spastic paraplegia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Rohan R. Mahale, Gautam Arunachal[1], Raviprakash Singh, Hansashree Padmanabha, Pooja Mailankody

Departments of Neurology and [1]Human Genetics, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India

Address for correspondence: Dr. Rohan R. Mahale, Department of Neurology, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India.
E-mail: rohanamahale83@gmail.com

References

1. Elsayed LEO, Eltazi IZ, Ahmed AE, Stevanin G. Insights into clinical, genetic, and pathological aspects of hereditary spastic paraplegias: A comprehensive overview. Front Mol Biosci 2021;8:690899. doi: 10.3389/fmolb. 2021.690899.
2. de Souza PVS, de Rezende Pinto WBV, de Rezende Batistella GN, Bortholin T, Oliveira ASB. Hereditary spastic paraplegia: Clinical and genetic hallmarks. Cerebellum 2017;16:525-1.
3. Shimazaki H, Honda J, Naoi T, Namekawa M, Nakano I, Yazaki M, *et al*. Autosomal-recessive complicated spastic paraplegia with a novel lysosomal trafficking regulator gene mutation. J Neurol Neurosurg Psychiatry 2014;85:1024-8.
4. Harding AE. Classification of the hereditary ataxias and paraplegias. Lancet 1983;1:1151-5.
5. Hazan J, Fonknechten N, Mavel D, Paternotte C, Samson D, Artiguenave F, *et al*. Spastin, a new AAA protein, is altered in the most frequent form of autosomal dominant spastic paraplegia. Nat Genet 1999;23:296-303.
6. Salinas S, Proukakis C, Crosby A, Warner TT. Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. Lancet Neurol 2008;7:1127-38.
7. Kaplan J, De Domenico I, Ward Dm. Chédiak-Higashi syndrome. Curr Opin Hematol 2008;15:22-9.
8. Uyama E, Hirano T, Ito K, Nakashima H, Sugimoto M, Naito M, *et al*. Adult Chédiak-Higashi syndrome presenting as parkinsonism and dementia. Acta Neurol Scand 1994;89:175-83.
9. Karim MA, Suzuki K, Fukai K, Oh J, Nagle DL, Moore KJ, *et al*. Apparent genotype-phenotype correlation in childhood, adolescent, and adult Chédiak-Higashi syndrome. Am J Med Genet 2002;108:16-22.

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