# A Novel Mutation of CAPN1 Gene Causing Hereditary Spastic Paraplegia-76

Dear Editor,

Hereditary spastic paraplegia (HSP) refers to a group of familial diseases that are characterized by progressive degeneration of the corticospinal tracts. Clinically, they present with gradually increasing lower limb spasticity and weakness, usually over many years after onset. Prevalence is low at about 3 to 10/100,000.[1]

Classification of HSP is increasingly based upon genetics, as there is phenotypic heterogeneity of HSP within the same family harboring the same genetic defect. The genetic classification of HSP is based upon mode of inheritance, chromosomal locus, and causative mutation. The genetic loci are designated as SPG (for "Spastic Paraplegia") and are numbered sequentially based on the order of locus discovery. HSP-76 is an autosomal recessive neurological disorder.[2] It is characterized by onset of slowly progressive spasticity of the lower limbs in young adults.

We evaluated a family of 8 affected individuals hailing from Belgaum District in Karnataka State, India, in the Neurology

Out-Patient Clinic of our Institute. The proband was a 30-year-old male, who was apparently normal till the age of 22 years. The first symptom he noticed was a tendency to drag his left lower limb while walking. Later, he noticed that his left lower limb would cross in front of his right while walking, resulting in slowness and change in his gait while walking. Over a period of few months, he started tripping over small obstacles. Gradually the symptoms appeared in his right lower limb, with slow progression. He developed progressive stiffness and weakness of both lower limbs with reduced range of movements at the joints.

Initially, he had no difficulty in getting up from squatting position or buckling of knees. He never had symptoms in his upper limbs and no incoordination, sensory, cognitive, or sphincter disturbances. Over a period of years, the patient gradually developed dysarthria, while his lower limb symptoms progressed for a while and subsequently plateaued. The patient was able to perform his activities of daily living on his own with difficulty and remained independent and ambulant without assistance.

Detailed family history revealed that multiple members of his family were affected [Figure 1]. The patient was born to a consanguineous marriage, and he was the third born child. His sibling brother is affected, while his sister is not. There are also several affected members in his extended family.

Higher mental functions including language were normal. There were no cranial nerve abnormalities. He had marked dysarthria characterized by slow, strained speech with slurring of syllables. He had prominent spasticity in the lower limbs, predominantly involving the hamstrings and adductors. Upper limb spasticity was milder in degree. He had Grade 4 power in all the limbs along with exaggerated deep tendon reflexes, ankle and patellar clonus and extensor response to the plantar reflex on both sides. Sensory system examination was normal. There was no in-coordination or ataxia. Skull and spine were normal. Gait testing revealed a slow, spastic paraparetic gait with prominent scissoring, but he could walk unassisted. There were no neurocutaneous markers.

Laboratory tests did not reveal any abnormalities in blood counts, electrolytes, renal, hepatic or thyroid functions. Vitamin B12 and erythrocyte folate levels were normal. Antiphospholipid, and anti-ds DNA antibodies were negative. He was negative for retroviral disease. Spinal and brain magnetic resonance imaging (MRI) was unremarkable. Nerve conduction study was normal, as were evoked potentials. Fundus and retina were normal.

In view of the clinical presentation, consanguinity and multiple affected family members, genetic testing was offered to this family. Whole exome sequencing was offered to the proband and subsequently targeted sequencing using selective capture and sequencing of the protein coding regions of the genomes/genes were performed on the variant of interest in the remaining family members. Exon 9 of CAPN1 gene was PCR amplified and the product was sequenced using Sanger sequencing.

The genetic study revealed the presence of a homozygous variant (c.1148 G > A; p.Gly383Asp) in CAPN1 gene, in the index patient. This variant was previously unreported in literature. Homozygous mutation in CAPN1 gene is known to cause HSP-76,[2] and hence this mutation is the most likely pathogenic variant in this family, thus confirming the diagnosis of HSP -76.

Detailed evaluation of his relatives with history, clinical examination and genetic testing was done [Table 1].

Gan-Or *et al*.[2] (2016) reported 3 families, 2 consanguineous Moroccan families and 1 non-consanguineous North

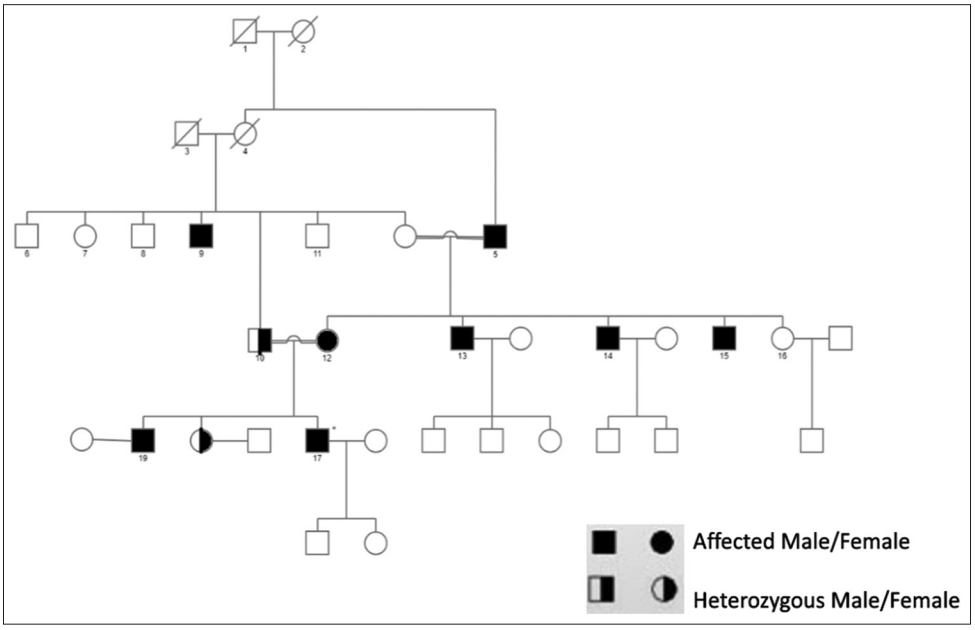


**Figure 1:** Pedigree Chart, with patients numbered serially from first-generation (Proband is patient number 17)

**Table 1: Clinical data, age of onset and genetic testing results of the affected family**

| Patient Serial No. | Clinical Presentation | Age of Onset | Speech | Other Symptoms or Signs | Genetic Testing |
|---|---|---|---|---|---|
| 17 | Mild | 22 | Mild | Foot Deformity, Sensory Symptoms | Positive |
| 5 | Moderate | 25 | Moderate | None | Positive |
| 9 | Mild | 24 | Normal | None | Positive |
| 12 | Severe | 21 | Mild | Urinary Symptoms Sensory-Motor Peripheral Neuropathy | Positive |
| 13 | Severe | 19 | Severe | Urinary Symptoms Sensory-Peripheral Neuropathy | Positive |
| 14 | Mild | 24 | Mild | Upper-limb Involvement | Not Tested |
| 15 | Mild | 25 | Mild | None | Not Tested |
| 19 | Moderate | 22 | Normal | Foot Deformity | Not Tested |

American family, with spastic paraplegia due to CAPN1 gene mutation. The clinical features of 8 patients were reported in detail. The average age at onset was 28.5 years (range 19 to 39); all affected individuals had spasticity and hyperreflexia of the lower limbs. Six patients had foot deformities, including pes cavus or pes valgus, 2 had abnormal bladder function, and 2 had distal sensory impairment. The motor impairment was mild to moderate, and 2 patients had started using a cane to aid in walking. There were no other neurologic abnormalities.

The proband has a homozygous mutation along with his mother, maternal uncle and elder brother and are hence affected. The father and elder sister are heterozygous and unaffected. The patient's spouse was also evaluated for this pathogenic mutation and was found to be negative and hence progeny will not be affected.

The current study is in concordance with previous studies that rare homozygous or compound-heterozygous mutations in *CAPN1* cause a complicated form of HSP.[3] Most of the affected individuals from these families suffer from additional neurological symptoms in addition to the typical spasticity of the lower limbs, such as upper-extremity hyper-reflexia, dysarthria, and gait ataxia.

CAPN1, located in chromosomal region 11q13, encodes calpain 1, also known as the large subunit of μ-calpain, a calcium-activated cysteine protease that is widely present in the CNS.[4] Calpain 1 is probably important for several functions in the CNS, but its exact role in humans is still not clear. Calpain 1 is involved in synaptic plasticity and several mechanisms for its function have been suggested in animal models.[5] For example, it was shown that Calpain interacts with CDK5 and NR2B to control NMDA-receptor degradation and synaptic plasticity.[6] However, there are contradicting results regarding the role of Calpains in neuroprotection and neurodegeneration, given that several studies suggest that calpain inhibition might be neuroprotective.[7] These features are also seen in other autosomal-recessive forms of HSP. For example, individuals with AR-HSP caused by mutations in *SPG7* often present with phenotypes very similar to those described in the current study, including symptoms such as dysarthria, ataxia, upper-extremity hyperreflexia, amyotrophy, pes cavus, and sensory neuropathy.[8,9]

HSP represents a heterogeneous group of diseases that may share a final common pathway in the neuronal degenerative process. This report presents a novel mutation in the CAPN1 gene, known to cause HSP 76. The phenotype of the affected individuals closely resembles that of a mild to moderate form of the disease with early onset and eventual plateauing. All patients in this family are on supportive and rehabilitative medical therapy and have mild to moderate morbidity and are living unassisted.

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## Conflicts of interest

There are no conflicts of interest.

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