# Myoclonus with hereditary axonal neuropathy: A novel phenotypic presentation of ATL3 mutation in a family from South India

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**TYPE OF ARTICLE:** Case Report

# Myoclonus with hereditary axonal neuropathy: A novel phenotypic presentation of ATL3 mutation in a family from South India

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## ABSTRACT

**Background.** Hereditary motor-sensory neuropathy (HMSN), also known as Charcot-Marie-Tooth (CMT), is a disorder characterized by chronic sensory and motor polyneuropathy, resulting in distal motor neuropathy. HMSN is genetically heterogeneous, with over 90 pathogenic genes identified. Myoclonus is an unusual association of HMSN.

**Case Report.** A 23-year-old female presented with myoclonic jerks since age 5, progressing to involve all four limbs. A few years later she developed insidious progressive distal predominant weakness of all four limbs. By age 15, she required a wheelchair. Examination revealed hypotonia, diminished reflexes, and distal muscle weakness. Genetic analysis identified a heterozygous missense variant in exon 9 of the ATL3 gene. Her brother exhibited similar symptoms and had similar mutation as well.

**Conclusions.** ATL3 mutations are associated with hereditary sensory neuropathy type I F. This case highlights a novel phenotypic presentation, including myoclonus and short stature, not

previously described with ATL3 mutations. Early diagnosis and genetic counseling are crucial for managing HMSN.

**Keywords:** Charcot-Marie-Tooth, ATL3 gene, hereditary motor-sensory neuropathy

**Abbreviations:**
CMT- Charcot-Marie-Tooth
HMSN- Hereditary motor-sensory neuropathy

## INTRODUCTION

Hereditary motor-sensory neuropathy (HMSN) also known as Charcot –Marie –Tooth (CMT) refers to a group of disorders characterized by chronic sensory and motor polyneuropathy which manifests as symmetric, slowly progressive distal motor neuropathy of arms and legs resulting in weakness and atrophy of muscles with deformities and sensory abnormalities. Based on clinical and electrophysiological findings, it is classified as axonal, demyelinating or intermediate types. CMT is a genetically heterogeneous disorder with numerous causative genes identified. The most common genetic pathogenic loci identified are PMP 22, MPZ, GJB1, and MFN 2[1]. With recent development and application of molecular genetics, more than 90 pathogenic genes have been discovered and reported. Myoclonus is an unusual association of HMSN. This report describes the clinical features of a 23-year female with HMSN phenotype atypically associated with myoclonus secondary to ATL3 gene mutation.

## CASE REPORT

A 23-year-old female, born out of a non-consanguineous marriage with normal birth and development history presented with complaints of involuntary jerks of upper limbs since the age of 5. The myoclonic jerks initially were present with a frequency of 1-2 per month, which gradually increased to a frequency of 10/day over the next few years and also progressed to involve all four limbs. It was not triggered by any sudden unexpected acoustic or tactile stimulus and was not associated with loss of awareness. At the age of 10 years, she was noted to have recurrent falls due to tripping of toes, associated with frequent slippage of footwear, which progressed to bilateral footdrop, requiring foot splints. At the age of 11, the patient noted difficulty in getting up, and climbing stairs, signifying proximal weakness. The patient also noticed upper limb distal weakness in the form of difficulty in gripping objects, and buttoning shirts, at the same time. There were no associated symptoms to suggest sensory, higher mental, cranial nerve, extrapyramidal or autonomic involvement. By the age of 15 years, the patient required a wheelchair for mobilization. The patient had a younger brother with developmental

delay, myoclonic jerks and distal predominant weakness in all four limbs since the age of 7 (Figure 1).

On examination, the patient had a short stature with clawing of hands and pes cavus foot deformity and an MMSE score of 26/30. Spinomotor examination revealed hypotonia in all 4 limbs, diminished reflexes, and an upper limb power of 3/5 (proximal and distal) and lower limb proximal power of 2/5 and distal power of 1/5. Trunk and neck muscles were normal. Sensory examination revealed mild impaired graded sensory loss to vibration and joint position. There were no witnessed jerks at present with extrapyramidal examination being normal.

Investigation revealed normal blood routines including hemogram, liver, renal, and endocrine parameters with normal ECG and 2d transthoracic echo. Her CPK levels were normal. Nerve conduction studies done previously at the age of 17 revealed, sensory-motor axonal neuropathy of all four limbs, with normal visual evoked potentials. A repeat nerve conduction study done now showed no recordable parameters. MRI Brain and whole Spine were normal.

Electroencephalogram (EEG) done earlier in the course of the disease had showed epileptiform discharges, for which antiepileptic drugs were started, but the EEG done presently was normal.

Genetic analysis was sent, which identified a heterozygous missense variant in exon 9 of the ATL3 gene (chr11:63411700; G>G/A) that results in amino acid substitution of serine for proline at codon 245. Hereditary motor sensory neuropathy 1F is caused by a heterozygous mutation in the ATL3 gene, but the present mutation was classified as a variant of unknown significance. So genetic sequencing of the brother and parents was done which showed c.733 C>T (Exon 9) in the ATL3 gene in all three family members (Figure 2).

## DISCUSSION

HMSN is a group of heterogeneous sensory and motor hereditary neuropathies. It was first reported by Charcot, Marie and Tooth in 1886 [2]. Individuals with CMT manifest symmetric, slowly progressive distal motor neuropathy of the arms and legs usually beginning in the first to third decade, resulting in weakness of feet and/or hands. Often associated with mild to moderate distal sensory loss. Various movement disorders have been described in the context of HMSN, such as tremor, Parkinsonism and dystonia. A postural/ action tremor in the upper limbs is commonly observed in patients with long-standing HSMN, reported in up to 40% of cases with CMT1A, the most common type of demyelinating CMT caused by duplication of the *PMP22* gene and in up to 20% of cases in CMT 2 caused by *MFN2* or *GDAP1* mutations with a delayed tremor presentation compared to neuropathy onset. Parkinsonism association is rare, although it has been reported in some HSMN patients with mutations in *LRSAM1*, *FIG4* and *SLC25A46*

genes with Parkinsonism appearing either simultaneously or following after a few years [3]. Myoclonus has not been described in relation to HMSN

Conditions that can have both peripheral neuropathy and myoclonus, include mitochondrial encephalopathic syndrome (particularly myoclonic epilepsy with ragged red fibers, Leigh syndrome, NARP, Kearns–Sayre syndrome and mitochondrial encephalomyopathy with lactic acidosis and stroke like episodes), Neuronal Ceroid lipofuscinoses, and spinocerebellar degeneration (particularly SCA-3). However, our patient did not have evidence of these disorders like regression of milestones, cognitive impairment, visual loss, nystagmus, late-onset ophthalmoplegia, and extrapyramidal features. Several associations of myoclonus with focal neuropathies have been described. In many, myoclonus is segmental or occurs in the territory innervated by the affected nerve, which is consistent with the ectopic generation of efferent motor impulses driving the movements. In others, spread of the movements to involve other muscles or sensory nerve involvement suggests that the central nervous system must generate the movements [4].

ATL3 gene encodes a member of dynamin-like, integral membrane GTPases, which is required for the formation of a network of interconnected tubules of the endoplasmic reticulum [5]. Mutations in this gene are associated with hereditary sensory neuropathy type IF [6]. To date, 2 different ATL3 gene mutations have been reported to be associated with hereditary sensory neuropathy type 1F (HSN 1F) which usually presents with significant sensory complaints and ulcers. However, our patient did not have significant sensory complaints or ulcerations and manifested other features like myoclonus and short stature. Genetic study in the family revealed similar mutation in the mother and the brother but a wild type probably non-pathogenic mutation in the father. The mother did not clinically exhibit sensory or motor signs or myoclonus, but did have a subtle difficulty in mobilizing and fatigue, which she attributed to her weight.
Apart from rehabilitation services, at present there is no definite treatment for HMSN. Early diagnosis and genetic counselling might influence positive lifestyle modifications and help in reducing the disability rate of disease.

## CONCLUSION

ATL3 mutations are known to cause hereditary sensory neuropathy type 1F (HSN1F), typically characterized by sensory neuropathy and associated complications such as ulcerations. This case, however, expands the clinical spectrum of ATL3 mutations by presenting a novel phenotype,

including myoclonus and short stature—features not previously documented in relation to ATL3 mutations.

**Patient consent:** obtained

**Conflict of interest:** The authors declare that they have no competing interests

**Authors' contributions:** Anuhya Chadalawada - data acquisition, interpretation, drafting; Rithvik Ramesh - Conception and design, data acquisition, interpretation, drafting and revision; Lavanya Kunkala - data acquisition, interpretation; Sundar. S - Conception, final approval; Lakshmi Narasimhan: Revising it for critical intellectual content, Final approval; Philo Hazeena: final approval; Deepa Avadhani: final approval.

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**FIGURES**

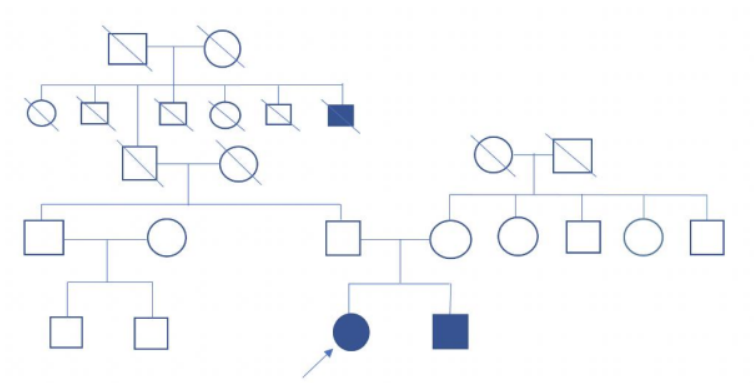

**Figure 1.** Family chart of the proband.

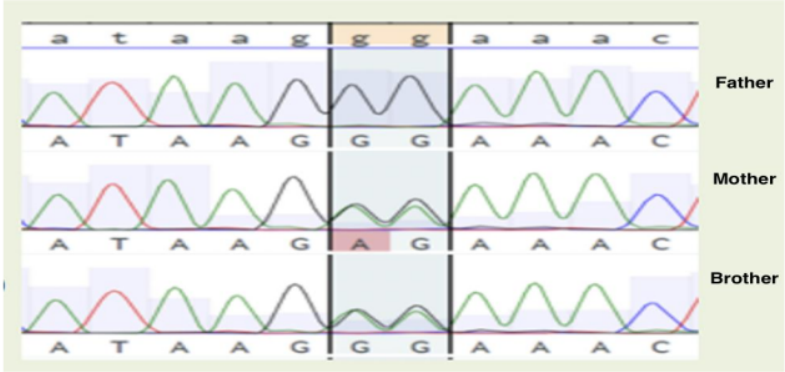


**Figure 2.** The genetic analysis of the proband's family. The father carries a wild type mutation in the same gene, and the mother and brother carry a possible disease-causing variant in the same gene.