# CAPN1

The CAPN1 gene, located on chromosome 11q13.1, is a protein-coding gene involved in neuronal plasticity, migration, microtubular regulation and cerebellar development. Several families with CAPN1 mutations have recently been reported to present with autosomal recessive (AR) HSP and/or ataxia.

METHOD: Patients with HSP were identified through neurological and genetic clinics with detailed phenotyping. Whole exome sequencing revealed novel pathogenic CAPN1 mutations in four patients from 3 families.

RESULTS: Affected families were of Turkish, Japanese, and Punjabi descent and all were consanguineous. Onset of spastic paraplegia in the four patients was between 20 and 37 years. Two also had mild ataxia. Three different novel, homozygous mutations in CAPN1 were found: c.2118+1G > T, c.397C > T, c.843+1G > C. The patient with the earliest onset also manifested profound muscle weakness, likely related to a second homozygous mutation in DYSF (dysferlinopathy).

CONCLUSIONS: The phenotype of AR CAPN1 mutations appears to be spastic paraplegia with or without ataxia; onset is most commonly in adulthood. Eye movement abnormalities, skeletal defects, peripheral neuropathy and amyotrophy can sometimes be seen. Occasionally, patients can present with ataxia, illustrating the genotypic and phenotypic overlap between HSP and spastic ataxia. With the advent of exome sequencing, mutations in more than one gene can be identified, which may contribute to the phenotypic variation, even within a family [1)].

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Hereditary spastic paraplegia (HSP) is a genetically and clinically heterogeneous disease characterized by spasticity and weakness of the lower limbs with or without additional neurological symptoms. Although more than 70 genes and genetic loci have been implicated in HSP, many families remain genetically undiagnosed, suggesting that other genetic causes of HSP are still to be identified. HSP can be inherited in an autosomal-dominant, autosomal-recessive, or X-linked manner. In the current study, we performed whole-exome sequencing to analyze a total of nine affected individuals in three families with autosomal-recessive HSP. Rare homozygous and compound-heterozygous nonsense, missense, frameshift, and splice-site mutations in CAPN1 were identified in all affected individuals, and sequencing in additional family members confirmed the segregation of these mutations with the disease (spastic paraplegia 76 [SPG76]). CAPN1 encodes calpain 1, a protease that is widely present in the CNS. Calpain 1 is involved in synaptic plasticity, synaptic restructuring, and axon maturation and maintenance. Three models of calpain 1 deficiency were further studied. In Caenorhabditis elegans, loss of calpain 1 function resulted in neuronal and axonal dysfunction and degeneration. Similarly, loss-of-function of the Drosophila melanogaster ortholog calpain B caused locomotor defects and axonal anomalies. Knockdown of calpain 1a, a CAPN1 ortholog in Danio rerio, resulted in abnormal branchiomotor neuron migration and disorganized acetylated-tubulin axonal networks in the brain. The identification of mutations in CAPN1 in HSP expands our understanding of the disease causes and potential mechanisms [2)].

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2)

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