

Hereditary Spastic Paraplegia 15 (SPG15)



Cure SPG15 Disease
Raising money to fund medical
research and awareness of
Hereditary Spastic Paraplegia 15



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SYMPTOMS OF SPG15

- Spasticity in lower limbs – Progression to upper limb involvement comes later
- Weak muscle tone
- Muscle Spasms
- Muscle wasting
- Difficulty walking
- Cognitive Issues causes learning difficulties and intellectual disability
- Ataxia
- Issues with bladder control
- Shuffling Gait
- Dystonia in some cases

Depending on the severity in patients, mutations in SPG15 can cause other neurological complications such as:

- Visual Impairment (Kjellin Syndrome)
- Parkinsonism
- Dementia
- Involuntary movements
- Dysarthria
- axonal neuropathy
- Seizures
- Abducted thumbs in some cases
- SPG15 seems clinically identical to another complicated Spastic Paraplegia, SPG11, both can present with juvenile parkinsonism. Emerging studies implicating these two proteins in interactions with the late endosomal/lysosomal adaptor protein complex AP-5 are consistent with shared abnormalities in lysosomes, supporting a converging mechanism for these two disorders.



TREATMENTS

There are currently **NO** specific treatments to prevent, slow, or reverse SPG15. Treatments tend to be supportive and target symptoms such as spasticity or bladder control issues. Examples of medication include muscle relaxants, sedatives to reduce spasms, and drugs to reduce overactivity of muscles.

Botulinum toxin injections can be helpful for targeting specific problematic muscle groups. Intrathecal baclofen therapy for the treatment of spasticity and gait improvement has also been a management option.

Regular physical therapy is **MOST** important for muscle spasticity and to try and preserve range of motion by improving strength and gait.

Levodopa should be considered for some patients affected with SPG15 that may include juvenile-onset levodopa-responsive parkinsonism.



WHAT CAUSES THE CONDITION

HEREDITARY SPASTIC PARAPLEGIA 15 (SPG15) is caused by mutations in the ZFYVE26 gene. It is an autosomal recessive disorder which means that both parents have passed on a mutation to defect the gene. The gene provides instructions for making a protein called spastizin, which is associated with the adaptor protein 5 (AP-5) complex. Spastizin is important in a process called autophagy, in which worn-out cell parts and unneeded proteins are recycled within cells.

As a result of these defective mutations autophagy is impaired and the recycling of materials within the cells is decreased. The inability to break down unneeded materials which accumulates in the cells can lead to cell dysfunction and often cell death. There is accumulating evidence that lysosomal and autophagic dysfunction are increasingly implicated in parkinsonism.

In almost all affected individuals with SPG15 the tissues in the brain are distinguished by prominent thinning of the corpus callosum which is correlated with cerebellar atrophy and disease severity in patients. There is loss of nerve cells in different parts of the brain. Neurodegeneration and white matter changes leading to cognitive decline and spasticity in SPG15 are often seen in other lysosomal disorders.

IMPACT OF THE CONDITION

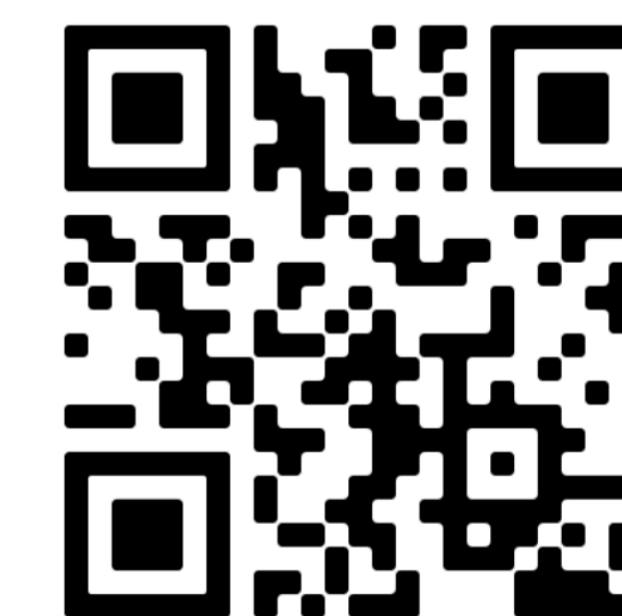
Most people with spastic paraplegia type 15 experience a decline in intellectual ability and an increase in muscle weakness and nerve abnormalities over time. As the condition progresses, many people require walking aids or wheelchair assistance in adolescence or adulthood.

The more complex it can be the more devastating it is for the patients and their families. The loss of motor functions affects all four limbs and cause severe cognitive impairments.

These patients may be unable to work, carry out day to day functions that is taken for granted and are unable to move around freely, they will have to rely on a carer to aid their needs. Some cases are very similar to patients with motor neuron disease (ALS) where body functions shut down. This reduces their quality of life.



FOR MORE INFORMATION
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HOPES & ASPIRATIONS FOR THE FUTURE

With autophagy being one of the affected pathways in SPG15 means this could lead to more understanding of new ways to treat Parkinson's patients. Some patients with SPG15 present with Parkinsonism as a symptom.

1. Gene Therapy research is already underway for SPG15 –
 - a. DNA were cloned in clinical lentiviral backbone. The viral vector has been validated in patient fibroblasts.
 - b. SPG15 cDNA has been split in 2 separate fragments and cloned in dual AAV vectors. The vectors are being fully characterised for transgene expression in cell lines and neurons isolated from mouse embryos. (If AAV dual strategy successfully produce SPG15 in neurons isolated from SPG15-/- embryos, the strategy will then be tested in the mouse model to generate the proof-of-concept).
 - c. Mini-SPG15 Gene: To determine the conservation of amino acid residues in the SPG15 protein across animals, an analysis has been performed to search for SPG15 in the genomes of 30 mammals and 18 additional multicellular animals. This will help identify the key domains for mini-SPG15 gene. Efforts are ongoing at SITraN to assess a mini-gene version of SPG15.
2. Research is underway to understand the biology of spastizin, how it associates with spatacsin (SPG11) and AP-5, and what controls its ability to function and this understanding might open new avenues for therapeutic targets/interventions not only to treat SPG15, SPG11 but also other HSP's and Parkinson's.
3. Testing GSK3β inhibitor on neuronal lines derived from iPSC of a patient with SPG11 and SPG15 and on gene-edited lines. This treatment rescued neuritic pathology in the cells and decreased cell death, suggesting a GSK3β inhibitor as a candidate for further translational work.
4. Early stages of testing efficiency in cells to promote translation read through of compounds that can rescue loss of spastizin protein.
5. To build a solid patient registry with a natural history study, it is important to develop a trial ready cohort to be able to take advantage of the development of therapeutic opportunities.