

New Gene Mutations May Help Identify Hereditary Spastic Paraparesis

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ARTICLE IN BRIEF

Investigators identified genetic mutations — and clinical symptoms — specific to hereditary spastic paraparesis that may make it easier to distinguish the upper motor neuron disorder from others, such as primary lateral sclerosis.

Dutch researchers have discovered mutations in patients with sporadic adult-onset spastic paraparesis (HSP) that may help differentiate them from patients with primary lateral sclerosis (PLS), an upper motor neuron disorder with similar symptoms. Unlike PLS, however, HSP does not appear develop into amyotrophic lateral sclerosis (ALS).

If confirmed by other studies, this information could be a useful first step in early identification of HSP patients.

Both dominant and recessive mutations in the *paraplegin* gene (*SPG7*) have been identified in patients with HSP, as have defects in the gene for *spastin* (*SPG4*).

The new study, published online Sept. 17 in advance of the print edition of *Neurology*, suggests that patients with adult-onset spastic paresis caused solely by defects in *SPG7* share certain characteristics, genetically and clinically, that are different than those in PLS patients, and therefore have a better prognosis.

Lead author Frans Brugman, MD, professor of neurology at Rudolf Magnus Institute of Neuroscience at the University Medical Center in Utrecht, the Netherlands, told *Neurology Today* that HSP and PLS are often confused, and telling them apart can be difficult.

HSP is a group of genetic disorders characterized by slowly progressive spastic paraparesis (leg weakness, gait disturbances, and spasticity), often accompanied by mental retardation, seizures, muscle spasms, sensory disturbance, and sphincter dysfunction.

PLS is also characterized by progressive weakness and spasticity of limb muscles, with mostly spinal and occasional bulbar region onset (dysphagia or dysarthria). Some autopsy reports have shown ALS pathology in PLS patients.

When patients without a family history of neurologic disease develop progressive spasticity, they can have HSP, remain spastic without a known cause, as in PLS,

or develop ALS.

The investigators had previously reported that the mutated *spastin* gene (*SPG4*) caused about 40 percent of autosomal dominant HSP, as well as 13 percent of sporadic HSP. In addition, mutations of the *paraplegin* gene (*SPG7*) are associated with autosomal recessive HSP in 1.5-6 percent of cases. *Paraplegin* is part of a mitochondrial protein family that plays a role in such cell processes as membrane trafficking and intracellular motility, protein folding, and proteolysis.

STUDY PROTOCOLS

For the current study, Dr. Brugman and colleagues screened 98 patients with sporadic adult-onset UMN syndromes in whom *spastin* mutations had been excluded. No mutations were found in 33

patients with UMN involvement in the bulbar region. But in 11 patients, they found nine sequence variants in the gene for *paraplegin* (*SPG7*), seven of which were completely new.

The seven patients had homozygous *paraplegin* mutations (identical defects at the same chromosome location) or compound heterozygous defects (different mutations at the same location). These cases were all recessive, while *spastin* mu-

Study Terms: At A Glance

- In autosomal dominant disease, there is one copy of a mutated gene and one normal gene in a pair of autosomal chromosomes. The risk of a parent passing the disease on to their offspring is 50-50.
- Autosomal recessive disease requires two copies of a defective gene in order for a disease to be inherited, and offspring have a one-in-four chance of inheriting the defect.
- Upper motor neuron disorders involve the motor region of the cerebral cortex or brain stem, where neurons connect the brain to the spinal cord. Lower motor neurons then carry signals to the appropriate muscles.

tations are dominant, so the defect occurs only on one chromosome.

Six of the seven patients had UMN symptoms restricted to the legs, and one person had symptoms in legs and arms. Three developed cerebellar signs during follow-up, but no such symptoms were detected in any of the patients without *paraplegin* mutations. If confirmed by other studies, this information could be a useful first step in early identification of HSP patients, as could age of onset, according to the authors.

“Our study shows that [these] mutations are a frequent cause in patients with adult-onset sporadic spastic paraparesis who are negative for *spastin* mutation, less so in patients who also have upper motor neuron (UMN) symptoms in the arms, and are absent in patients with UMN involving the bulbar region,” Dr. Brugman explained.

CLINICAL SCREENING

He said the results support offering *paraplegin* gene analysis, after exclusion of *spastin* gene mutation, to sporadic patients with an unexplained UMN syndrome, especially patients lacking bulbar UMN symptoms, younger patients, and those who develop cerebellar symptoms.

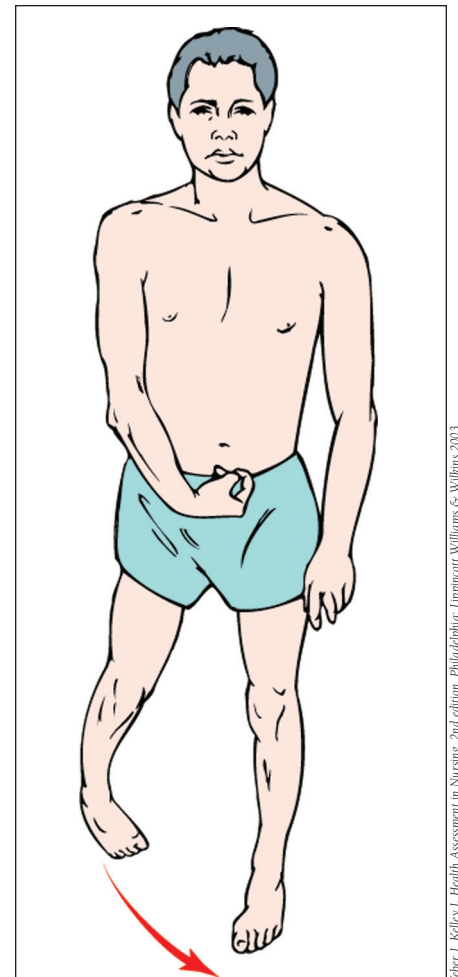
HSP patients sometimes develop cerebellar findings, as in these *paraplegin* cases, or a neuropathy. However, none of the patients in the new study had neuropathy, he noted.

The study authors advised: “Finding causative mutations is important both from a diagnostic and prognostic point of view. Genetic counseling can be offered to the patient and family members. Patients can be told that they have HSP, not PLS, and can be reassured that progression to ALS, as may occur in PLS, is not to be expected. The specific clinical features of *SPG7* can be discussed with the patient, including the possibility of developing a complicated HSP phenotype, which could cause additional disability compared to pure HSP.”

The findings suggest that almost all patients with pure HSP have symptoms restricted to the legs, with earlier onset. Those with more complicated HSP, caused by mutations in *SPG7*, *SPG4*, or other genes, may also develop cerebellar or upper limb motor symptoms.

Christopher McDermott, PhD, Honorary Consultant Neurologist at the Royal Victoria Infirmary, Newcastle upon Tyne, UK, had led several studies focusing on *paraplegin* mutations.

He said that the new findings add to the limited amount of evidence on such mutations and their role in the UMN dis-



THE ABNORMAL GAIT of spastic paraparesis.

orders. “This is an interesting paper which helps to further characterize the sporadic spastic paraparesis group of patients, who for many years have been difficult to diagnose,” he commented in an e-mail message to *Neurology Today*.

“As the authors note, an earlier and precise diagnose enables appropriate counseling regarding prognosis and risk to other family members as well as the avoidance of many unnecessary investigations.” •

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