

# Novel Mutation in SACS Gene in a Patient with Autosomal Recessive Spastic Ataxia Charlevoix-Saguenay

Igor Petrov, PhD\*

Charlevoix-Saguenay (ARSACS) is a rare autosomal recessive spastic ataxia.<sup>1</sup> The disease is characterized by progressive ataxia, pyramidal involvement, peripheral neuropathy and hypermyelination of the retinal nerve fibers due to the mutation in the SACS gene, SACS that encodes protein saccin. First mutations in the gene were found in French Canadians from the Saguenay region.<sup>2</sup>

A fifty-three-year-old Macedonian right-handed woman born from non-consanguineous parents, who was hospitalized at the Movement disorders department in Skopje, was complaining of progressive gait disturbance, walking difficulties, speech problems, changes in her mood, and slowness of performing her daily activities. Her first symptoms of depression began in 2004, at the age of 37 years, when she had an unsuccessful attempt of suicide for which she was hospitalized in psychiatric clinic in Negorci. Her sister also committed suicide. Around one year after this she developed progressive speech and gait difficulties. There were no other medical conditions of note. Her brother had similar symptoms.

Neurological examination revealed severe gait ataxia, and she was unable to walk tandem and had a broad base. Her speech was dysarthric and slurred. There was spasticity in the legs. Romberg sign was positive. Deep tendon reflexes were increased with extended reflexogenic area and Babinski sign was bilaterally positive. This patient had pyramidal signs as well as moderate bradykinesia and hypomimia.<sup>3</sup> (Video 1) She had late onset ataxia and the cognitive decline that was shown on the neuropsychological tests is novel in this case.<sup>4</sup>

MRI of the brain revealed bilateral cerebellar atrophy and a large arachnoidal cyst in the posterior cranial fossa in the projection of the cisterna magna. Occipital bilateral cortical atrophy is also seen (Fig. 1).<sup>5</sup> Electromyography (EMG) and nerve conduction studies revealed distal lower limb predominant peripheral axonal neuropathy. Somatosensory evoked potentials (SEP) on the tibial nerve showed prolonged latencies of the cortical waves.

Visual evoked potential (VEP) was normal. Electroencephalography (EEG) was normal. Cerebrospinal fluid analysis (CSF) showed slight elevation in the total protein, elevation in the albumin fraction and IgG and the type of electropherogram was transudative suggesting seepage through the blood brain barrier. Routine laboratory tests and routine blood tests were normal.



**Video 1.** 53 years old woman with autosomal recessive spastic ataxia Charlevoix-Saguenay. Ataxia, dysarthria, bilaterally positive Babinski sign, increase deep tendon reflexes and positive Romberg sign is presented. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13216>

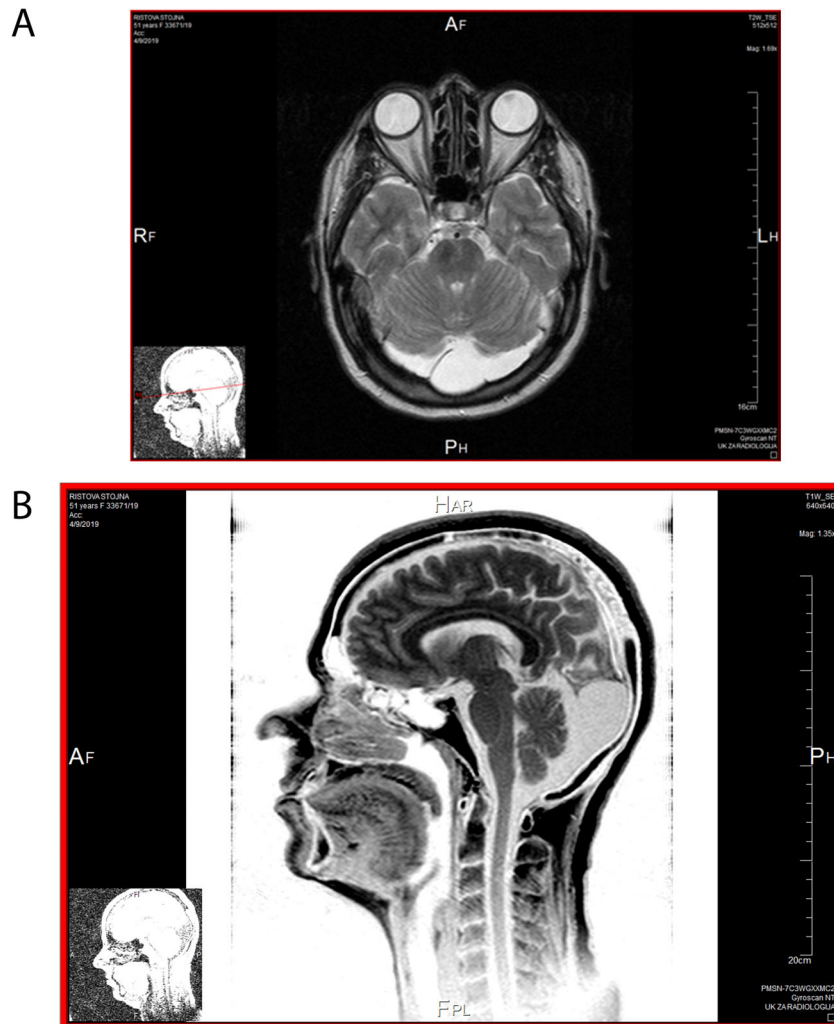
*Movement Disorders Department, University Neurology Clinic, Skopje, Republic of North Macedonia*

\***Correspondence to:** Dr. Igor Petrov, Movement Disorders Department, University Neurology Clinic, Vodnjanska 17, 1000 Skopje, Republic of North Macedonia; E-mail: [neuromed211@yahoo.com](mailto:neuromed211@yahoo.com)

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**FIG. 1.** MRI of the brain of the 53 years old woman with autosomal recessive spastic ataxia Charlevoix-Saguenay. (A) Bilateral cerebellar atrophy and large arachnoid cyst in posterior cranial fossa exactly in the projection of cisterna magna. (B) Cerebellar atrophy.

Genetic testing was performed. Targeted re-sequencing of 4800 clinically significant genes was made using TruSight One kit, Illumina and bioinformatic processing of the genes associated with the clinical condition of the patient.

The patient's genotype is NM\_014363.5:c.(13721T > G); (13721T > G). Pathogenic change c.13721 T > G;p (Phe 4574Cys) in the SACS gene was found. The patient is homozygous for pathogenic change c.13721 T > G;p. (Phe4574Cys) in SACS gene. This variant in exon 10 of SACS gene is missense variant that on protein level cause change of aminoacid phenylalanine on position 4574 in the aminoacid cystein. This is a novel variant that has not been published in the literature so far, and it is not present in the database of pathogenic variants of SACS gene. The change is in the recessive gene in homozygous form. A similar genetic finding was also detected in a homozygous state in the patient's brother who has a similar clinical manifestation of the disease. This genotype

confirmed the diagnosis of autosomal recessive spastic ataxia of Charlevoix-Saguenay in the patient and her brother. The genetic testing was made in the Macedonian Academy of Science and Art (MANU) in Skopje, Republic of North Macedonia.

The patient was treated with low doses of levodopa carbidopa with minimal effect on her bradykinesia.

The novelty in this article is that it is presented a patient from Republic of North Macedonia in whom a novel missense pathogenic variant c.13721 T > G;p. (Phe4574Cys) in SACS gene was found which has not been published in the literature before.<sup>6,7,8</sup> The patient had mild cognitive decline, moderate bradykinesia, and hypomimia with ataxia of late onset.

Duquette et al. found that in the clinical picture increased deep tendon reflexes are more common than spasticity, and neuropathy became more apparent in the second decade. Despite a homogeneous genetic background, some patients showed no signs of

neuropathy or spasticity by the age of 18 years.<sup>9</sup> In the patient described here she had clear spasticity and has been symptomatic at a late age.

Synofzik et al. found on MRI pontine hypointensities, all patients (100%) showed hyperintensities of the lateral pons merging into the (thickened) middle cerebellar peduncles. In addition, 63% exhibited bilateral parietal cerebral atrophy, and 63% a short circumscribed thinning of the posterior midbody of the corpus callosum.<sup>5</sup>

Hara et al. found that two patients had a unique phenotype characterized by dementia, ophthalmoplegia, and the absence of prominent retinal myelinated fibers.<sup>10</sup> In the patient described in the article, VEP was normal and there were no visual difficulties.

## Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

I.P.: 3A, 3B

## Disclosures

**Ethical Compliance Statement:** The author confirms that the patient provided written consent, consenting to use for educational purposes, but because this article is a case report, no IRB approval was necessary. I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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