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CASE REPORT

A Novel Exon Duplication in the *SACS* Gene in Charlevoix-Saguenay Ataxia and a Summary of Polish Cases

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Abstract: Mutations in the *SACS* gene are associated with autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), a clinically and genetically heterogeneous neurodegenerative disorder. ARSACS typically manifests as slowly progressive ataxia with spasticity and sensorimotor neuropathy. Nevertheless, an array of additional features may also be observed, including hearing impairment, epileptic seizures, and even the absence of spasticity. Reports of *SACS* mutations in Polish patients are rare. Here we report a compound heterozygous pathogenic variants in the *SACS* gene, a novel duplication of exon 6, and a frameshift deletion c.12923_12927del 12921_12925del p.(Lys4308SerfsTer21) in a Polish patient presenting with progressive ataxia, spasticity, and peripheral neuropathy. This is the first case with a rearrangement of a complete single exon of the *SACS* gene. We also review six previously described Polish individuals with *SACS* variants, noting that all presented with cerebellar ataxic gait and cerebellar atrophy on brain MRI scans. Across these cases, nine rare pathogenic *SACS* variants were identified. This study adds to the ARSACS-associated mutation spectrum, provides further insights into genotype-phenotype correlations, and highlights the importance of testing for structural variants.

Keywords: ataxia, neurodegeneration, diagnostics, next generation sequencing, CNV, expression

Introduction

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is one of the most prevalent forms of autosomal recessive ataxia caused by biallelic pathogenic variants in the *SACS* gene (OMIM: 270550).[1] Patients with ARSACS typically exhibit three core features: early-onset cerebellar ataxia, spasticity, and peripheral neuropathy. Additional atypical manifestations may include absence of spasticity, cognitive impairment, epileptic seizures, and hearing loss. Brain magnetic resonance imaging (MRI) often shows distinct cerebellar atrophy and linear T2 hypointensity within the pons, whereas optical coherence tomography (OCT) frequently shows retinal nerve fiber layer (RNFL) hypertrophy. However, some ARSACS cases lack these remarkable findings on brain MRI or retinal OCT.

Sacsin is a large 520kDa protein expressed ubiquitously but is enriched in neurons.[2] Although it's exact function is not fully understood it may play a role in recruitment or retention of Drp1 at mitochondrial fission sites, with loss of sacsin function leading to impaired mitochondrial activity.[3] Over 500 different pathogenic variants have been identified in the *SACS* gene,[4] with three-quarters occurring in exon 10, one of the largest in the human genome. Most mutations are frameshift inserions/deletions, or single nucleotide mostly nonsense variants with only two structural variants within *SACS* gene reported in Clinvar so far. The same mutations can lead to variable clinical presentations, sometimes even

Received: 3 July 2025
Accepted: 11 December 2025
Published: 24 December 2025

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within a single family. This clinical and genetic heterogeneity in ARSACS may complicate the accurate diagnosis. Herein, we report the case of a Polish patient with a novel *SACS* duplication of the entire exon 6 and a known small deletion, presenting with progressive ataxia and demyelinating peripheral neuropathy.

Case Report

Patient

A 22-year-old woman with a clinical diagnosis of spinocerebellar ataxia was referred to the Genetic Counselling Unit of the Institute of Psychiatry and Neurology in Warsaw. She was born at term via caesarean section due to breech presentation. The birth weight was 3200 g, the length was 57 cm, and the Apgar score was 9. Neonatal examination results were unremarkable. Early motor milestones were within the normal range; she sat independently at seven months and began walking at 13–14 months. However, signs of motor dysfunction, including difficulties in toe walking and balance, appear in early childhood.

By the age of 10, she exhibited high-arched feet (pes cavus), unsteady gait, and tight Achilles tendons. These signs were initially attributed to the perinatal complications. Despite motor issues, cognitive development remained normal. She completed higher education and earned a master's degree in pedagogy, maintaining employment as an office worker until the age of 31.

At 22 years of age, neurological evaluation revealed subtle horizontal nystagmus in the lateral gaze and incomplete convergence of the left eye. In general, muscle strength was preserved, but tone was significantly decreased. In the upper limbs, tendon and periosteal reflexes were reduced, with slight intention tremor on finger-nose testing, and dysdiadochokinesia. In the lower limbs, the patient showed calf hypertrophy, Achilles tendon contractures, and pes cavus, with limited ankle mobility. Knee reflexes were barely present and Achilles reflexes were absent. Babinski sign was positive. Coordination tests revealed slight dysmetria on heel-to-knee testing, and balance was impaired, as demonstrated by a positive Romberg test and broad-based, uncertain gait. She could walk on tiptoes but not on heels, consistent with the shortened Achilles tendons. Mild dysarthria was noted, but it was non-progressive.

Electrophysiological studies confirmed a diagnosis of sensorimotor peripheral neuropathy. Laboratory testing revealed mildly but persistently elevated creatine kinase levels. Brain and spinal magnetic resonance imaging (MRI) at the age of 12 years showed moderate cerebellar and cervical-thoracic spinal cord atrophy. EMG at 21 years revealed both demyelinating and axonal changes in the motor and sensory fibers of the peripheral nerves.

At the most recent follow-up at 39 years of age, the patient reported mild progression of ataxia and worsening foot deformities. She used elbow crutches for ambulation and underwent orthopedic surgery for Achilles tendon elongation.

Next-Generation Sequencing

DNA was extracted from the peripheral blood of the proband by using standard methods. Whole exome sequencing (WES) was performed commercially at the BGI Tech Solutions (Hong Kong) using the SureSelect Human All Exon v5 + UTR enrichment kit and paired-end 100 nt sequencing on the Illumina HiSeq2000 platform, as described previously.[5]

The SNVs and indels were initially filtered for a Phred quality score of at least 30. Only variants with an impact on the coding regions were retained for further consideration: missense, nonsense, frameshift, and essential splice site mutations. Further filtering was based on allele frequency in the ExAC (Exome Aggregation Consortium) database (< 1%), association with HPO (Human Phenotype Ontology) terms, and predicted pathogenicity. The HPO terms used were: "ataxia" and "neuropathy". Variants predicted to be pathogenic by at least one of the following programs were considered: MutationTaster, PolyPhen2, and SIFT. The remaining variants were confirmed by Sanger sequencing.

In total, 20 variants SNVs and indels passed filtering and prioritization (Supplementary Table 1). All of them were absent in 306 exomes and genomes from individuals of Polish origin deposited in our laboratory database. The *SACS* c.12923_12927del and *VCP* c.1460G>A variants were confirmed using Sanger sequencing in the proband (Table 1). The *SACS* variant was found in the proband's mother, and the *VCP* variant in her father.

A targeted ataxia panel analysis was additionally performed. The DNA library was prepared using the KAPA HyperPlus Kit and MiSeq 2×75 bp paired-end sequencing was performed using the MiSeq Reagent Kit v3 (150 cycles)

Table 1 Putative Causative or Phenotype-Modifying Genetic Variants Identified in the Proband

Hg38 Position	Gene	HGVS.c / HGVS.p	Genotype	dbSNP	gnomAD AF	ClinVar	ACMG Classification	Prediction Software
9:35060823	*VCP*	c.1460G>A p.(Arg487His)	Heterozygous C/T	rs767379602	6.20e-7	Conflicting interpretations	Uncertain Significance: PM2, PP3, BP4	CADD phred: 29.9, Alpha missense: benign, SIFT: deleterious low confidence, PolyPhen: possibly damaging, MeraLR, MetaRNN, MetaSVM, PROVEAN, fathmm-XF: damaging, Mutation Assesor: medium, MutationTaster: disease causing
13:23330948	*SACS*	c.12923_12927del p.(Lys4308SerfsTer21)	Heterozygous CTTCTT/C	rs1057517294	2.48e-6	Pathogenic	Pathogenic: PVS1, PP5, PM2, PM3	No data available (indel variant)

Note: cDNA and protein alterations are reported in *VCP* NM_007126.3 and *SACS* NM_014363.6.
Abbreviations: HGVS, Human Genome Variation Society; ACMG, American College of Medical Genetics and Genomics.

according to the manufacturer's procedure as described previously.[6] The targeted gene panel included the coding sequence of 152 known genes associated with hereditary ataxias, hereditary spastic paraplegias, and rare disorders presenting with ataxia symptoms. The results confirmed the Whole Exome Sequencing results, including *SACS* c.12923_12927del and *VCP* c.1460G>A variants, indicating no additional putative pathogenic variants.

Multiplex Ligation-Dependent Probe Amplification

SALSA MLPA Probemix P441 *SACS* (MRC Holland, Netherlands) was used to determine the presence of microrearrangements (exon deletion/duplication) in the *SACS* gene in the patient and her relatives. MLPA was performed according to the manufacturer's protocol and analyzed using a Coffalyser.net (MRC Holland, Netherlands). The results revealed the presence of the NM_014363.6:c.(345+1_346-1)_(457+1_458-1)dup covering exon 6 of the *SACS* gene in the patient and her father.

RNA Sequencing

Total RNA was isolated from the peripheral blood mononuclear cells of the proband, her parents, and controls (without neurodegenerative disorders nor *SACS* rare variants) using the RNeasy Mini Kit (Qiagen) according to the manufacturer's protocol. Total RNA (500 ng) was converted to cDNA libraries using TruSeq Stranded Total RNA with a Ribo-Zero kit (Illumina, Analityk Genetyka, Warsaw, Poland) according to the manufacturer's protocol. Libraries were assessed qualitatively on a Bioanalyzer 2100 using a High-Sensitivity DNA Kit, quantitatively on a CFX96 Real-Time PCR system (Bio-Rad) using the KAPA Library Quantification Kit (Kapa Biosystems), and then sequenced at 2×76 bp on a HiSeq2500 Illumina platform. Sequencing data were analyzed according to previously described protocols.[7]

Although the observed decrease in *SACS* mRNA expression in carriers of *SACS* variants was not statistically significant, the change was greatest in the proband with variants on both alleles. (Table 2). RNA sequencing also confirmed a heterozygous five-nucleotide deletion within the *SACS* exon 10 in the proband and her mother.

Table 2 *SACS* RNAseq Fold Change, with p-values in Brackets

	vs Father	vs Mother	vs Both Parents	vs Controls
Proband	0.8495 (0.544)	0.9721 (0.934)	0.9084 (0.725)	0.6704 (0.171)

Discussion

We present the fourth case and seventh Polish patient with a clinical and morphological diagnosis of ARSACS carrying a compound heterozygous mutation in the *SACS* gene.

Twenty rare genetic variants that might be associated with the disease were identified in the proband (Supplementary Table 1). The interpretation of identified variants was made according to the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) Standards and Guideline.[8] To assess the clinical significance of DNA variants ClinVar and ClinGen databases were used, whereas the population frequency of the variants was determined by gnomAD v3.1.2 (Genome Aggregation Database).

The *VCP* variant, although predicted by most programs as possibly damaging, does not match the symptoms well. This ultra-rare variant has been found in Japanese patients with amyotrophic lateral sclerosis (ALS),[9] but there are conflicting reports in Clinvar database. Pathogenic *VCP* mutations are known to cause inclusion body myopathy (IBM) with Paget's disease (PDB) frontotemporal dementia (FTD), FTD with amyotrophic lateral sclerosis (FTDALS6), and Charcot-Marie-Tooth Disease type 2Y (CMT2Y). Of these, only CMT2Y has peripheral neuropathy; however, the clinical presentation of the patient is not limited to polyneuropathy. Furthermore, a healthy father with no neurodegenerative disorders was found to be a carrier of the *VCP* variant. Although so called incomplete penetration of some *VCP* variants has been reported, this is uncommon and unlikely. The *SACS* variant was the only variant that fully matched the proband's clinical and morphological phenotypes. As *SACS* variants are responsible for autosomal recessive ataxia, identification of a single nucleotide variant is not sufficient for genetic diagnosis. Therefore, ataxia-targeted panel and subsequently MLPA analyses were performed. The duplication of exon 6 found both in the patient and her father is assumed to be a tandem duplication, thereby disrupting the open reading frame and resulting in p.(Pro154IlefsTer14) protein sequence change. Together with the frameshift variant c.12923_12927del, p. Lys4308SerfsTer21, found in both the patient and her mother, it plausibly explains the cause of the disease, however this was not confirmed by any functional studies.

The *SACS* mRNA level in the proband is two-thirds of that in healthy controls without rare *SACS* variants. Both parents also have reduced mRNA levels, although less significantly, to (on average) three quarters of the controls. A nonsense-mediated decay is the most plausible explanation as both variants introduce stop codons more than 50 nucleotides upstream of the last exon-exon junction. Lower expression in the father carrying exon duplication than in the mother with a frameshift variant (Table 2). Thus, our observations are consistent with previous studies of *SACS* expression in both ARSASC patients and carriers of a single heterozygous pathogenic *SACS* variant.[10]

This is the fourth Polish ARSACS case and the seventh patient described (Table 3).[6,11] Among them, were four women and three men. The age of first symptoms in all described cases was in early childhood, with slow disease progression. All patients had ataxia, five of them had spastic gait, one patient showed an absence of spasticity, all patients showed pes cavus, and five patients presented with peripheral neuropathy. All of them revealed cerebellar atrophy on the brain MRI. In five patients, MRI displayed signal hypointensities within the pons, and four showed thickening of the RNFL.

All patients carried compound heterozygous mutations in the *SACS* gene. A total of nine *SACS* gene mutations were identified, including three missense mutations, one nonsense mutation, three small deletions, one small insertion, and one gross duplication. The ACMG criteria resulted in mostly pathogenic of likely pathogenic classification, with only one missense classified as of uncertain significance. In the latter variant more pathogenic than benign criteria were met. Except for a gross duplication, all other mutations were identified in exon 10 of the *SACS* gene, which is a hotspot for pathogenic *SACS* mutations.[12] This localization of variants might not be surprising, as exon 10 is by far the largest one spanning almost 13kb - 80% of the coding sequence. However, we did not identify that many rare or uncommon non-pathogenic variants located in this exon in our in-house database. Of the 16 such variants, only nine were found in exon 10, while five were found in the second-largest exon 8, one in exon 6, and one in the intronic region adjacent to exon 3 (Table 4).[5,6,13,14] Many rare *SACS* variants were found in the Polish population, and some were more common than in the GnomAD non-Finnish European cohort (eg rs147099630 MAF was 0,8% in GnomAD NFE, and 4,7% in our in-house database), albeit usually with no phenotypic consequences.

Table 3 Polish SACS (NM_014363.6) Putative Pathogenic Variants Detected in Clinically Diagnosed ARSACS Patients

c.DNA	Protein	Novel/ Known	ACMG Classification	ACMG Criteria	rs id	GnomAD AF	Onset	Ataxia	Spasticity	Poly Neuropathy	Dysarthria	Babinski Sign	Cerebellar Atrophy	Spinal Cord Atrophy	Signal Hypointensity	Pubmed id
c.12923_12927del	p.(Lys4308SerfsTer21)	Known	Pathogenic	PVS1, PP5, PM2, PM3	rs1057517294	2.48e-6	10	+	+	+	Mild	+	+	Cervical-thoracic		Current case
c.(345+1_346-1)_(457+1_4581)dup	p.(Pro154IlefsTer14	Novel			–	–										
c.5773_5779delCTGAGTG	p.(Leu1925SerfsTer11)	Novel	Pathogenic	PVS1, PM2, PM3	–	–	20	Cerebellar and gait ataxia	–	–	–	–	+		+	35588347
c.11374C>T	p.(Arg3792Ter)	Known	Pathogenic	PVS1, PP5, PM2, PM3	rs565203731	6.20e-6										
c.5498C>T	p.(Ser1833Phe)	Novel	Uncertain	PM3, PM2, PP3, BP1	rs758464505	–	ND	+	ND	ND	ND	ND	ND	ND	ND	
c.7960T>G	p.(Tyr2654Asp)	Novel	Uncertain	PM3, PP3, PM2, BP1	–	–										
c.8340delT	p.(His2781MetfsTer4)	Novel	Pathogenic	PVS1, PP5, PM2	–	–										
c.9804_9805insC	p.(Ser3268_Ile3269fs)	Novel	Likely pathogenic	PVS1, PM2	–	–	1,5	Cerebellar, gait, limb ataxia	In the lower limbs	Peripheral	+	+	Severe	Cervical	+	28843771
c.12574G>A	p.(Asp4192Asn)	Novel	Uncertain	PM3, PP3, PM2, BP1	rs1188251236	6.20e-6										
c.9804_9805insC	p.(Ser3268_Ile3269fs)	Novel	Likely pathogenic	PVS1, PM2	–	–	4	Cerebellar, gait, limb ataxia	In the lower limbs	Peripheral	+	+	Severe	Cervical	+	
c.12574G>A	p.(Asp4192Asn)	Novel	Uncertain	PM3, PP3, PM2, BP1	rs1188251236	6.20e-6										
c.9804_9805insC	p.(Ser3268_Ile3269fs)	Novel	Likely pathogenic	PVS1, PM2	–	–	2	Cerebellar, gait, limb ataxia	In the lower limbs	Peripheral	+	+	Severe	Cervical	+	
c.12574G>A	p.(Asp4192Asn)	Novel	Uncertain	PM3, PP3, PM2, BP1	rs1188251236	6.20e-6										
c.9804_9805insC	p.(Ser3268_Ile3269fs)	Novel	Likely pathogenic	PVS1, PM2	–	–	5	Cerebellar, gait, limb ataxia	In the lower limbs	Peripheral	+	+	Severe	Cervical	+	
c.12574G>A	p.(Asp4192Asn)	Novel	Uncertain	PM3, PP3, PM2, BP1	rs1188251236	6.20e-6										

Abbreviations: ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; ACMG, American College of Medical Genetics; ND, no data.

https://doi.org/10.2147/TACG.S549120

Table 4 Polish SACS (NM_014363.6) Variants of Unknown Significance (VUS)

c.DNA	Protein	Novel/Known	ACMG Classification	ACMG Criteria	rs id	GnomAD NFE AF	Onset	Disease	ARSACS Symptoms	Pubmed id
c.3408T>G c.171+6C>T	p.(Asn1136Lys) ?		Likely benign Benign	BP1, BP4, PM2 BA1, BP6, BP4	rs756303420 rs3751368	8.68e-6 1.63e-1	60	Ataxia	Limbs and gait ataxia, dysarthria, pyramidal signs, tremor	35588347
c.2983G>T c.11066C>A	p.Val995Phe p.Pro3689Gln	Known Novel	Likely benign Uncertain significance	BP6, BS1, BS2, BP4, BP1 PM2, PP3, BP1	rs142967124 rs148925505	2.21e-3 1.529e-05		LGMD	–	29970176
c.1640C>T c.4015A>C	p.Pro547Leu p.Ile1339Leu	Known Novel	Likely benign Benign	BP4, BP1, PM2 BS1, BS2, BP4, BP1	rs140507581 rs143144795	4.27e-5 4.95e-4		LGMD	–	29970176
c.2080G>A c.4076T>C	p.Ala694Thr p.Met1359Thr	Known Known	Benign Benign	BS1, BS2, BP4, BP6, BP1 BS1, BS2, BP4, BP1, BP6, PP5	rs17325713 rs146451611	3.14e-2 1.95e-3		MFM	–	33652732
c.13717A>C	p.Asn4573His	Known	Benign	BS1, BS2, BP4, BP1, BP6	rs34382952	4.41e-3		LGMD	–	29970176
c.11032C>G	p.Pro3678Ala	Known	Benign	BA1, BP6, BP4, BP1	rs17078601	2.83e-2		GTS, LGMD	–	37208127
c.8339T>G	p.Phe2780Cys	Known	Benign	BS1, BS2, BP4, BP1, BP6	rs111540787	4.82e-3		LGMD	–	29970176
c.4466A>G	p.Asn1489Ser	Known	Benign	BS1, BS2, BP4, BP1, BP6	rs147099630	7.71e-3		GTS, LGMD	–	37208127
c.1373C>T	p.Thr458Ile	Known	Benign	BS1, BS2, BP4, BP1, BP6	rs61729954	2.13e-3		LGMD	–	29970176
c.1081A>G	p.Lys361Glu	Novel	Likely benign	BP4, BP1, PM2	rs377027736	1.23e-4		LGMD	–	29970176
c.751G>A	p.Val251Ile	Novel	Likely benign	BP4, BP1, PM2	rs776176699	5.58e-6		GTS with Schizophrenia	–	37208127
c.432G>T	p.Trp144Cys	Novel	Uncertain significance	PM2, BP1	rs368570790	6.39e-5		LGMD	–	29970176

Abbreviations: ACMG, American College of Medical Genetics; ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; LGMD, Limb-Girdle Muscular Dystrophy, MFM, Myofibrillar Myopathy; GTS, Gilles de la Tourette Syndrome.

Conclusion

The development and widespread use over the past two decades of next-generation sequencing (NGS) methods and algorithmic methods for prioritizing genomic variants identified by NGS allowed quicker genetic diagnosis but also changed the way that inherited diseases are viewed. It has become clear that often more than one gene may be associated with a given disease, different variants in a given gene can cause different phenotypes, and some variants are associated with multiple clinical phenotypes. The presented results indicate that also testing for rearrangements should be performed in patients in whom only one heterozygous mutation was detected. Only the combined use of these two approaches has enabled the establishment of genetic diagnosis.

Abbreviations

ACMG, American College of Medical Genetics and Genomics; AMP, Association for Molecular Pathology; ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; CMT2Y, Charcot-Marie-Tooth Disease type 2Y; ExAC, exome aggregation consortium; FTD, frontotemporal dementia; FTDALS6, frontotemporal dementia amyotrophic lateral sclerosis; gnomAD, Genome Aggregation Database; HGVS, Human Genome Variation Society; HPO, Human Phenotype Ontology; IBM, inclusion body myopathy; MLPA, multiplex ligation-dependent probe amplification; MRI, magnetic resonance imaging; OCT, optical coherence tomography; PDB, Paget's disease of bone; RNFL, retinal nerve fiber layer; SNV, single nucleotide variant; UTR, untranslated region; VUS, variant of unknown significance; WES, whole exome sequencing.

Ethics Approval

The study was approved by the Ethics Committee of the Institute of Psychiatry and Neurology in Warsaw, Poland in Decision 16/2009 and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. No additional institutional approval was required for the publication of this case report. The proband and her parents gave the written informed consent for testing and to have the clinical and genetic results published.

Disclosure

The authors report no conflicts of interest in this work.

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