Orphanet Journal of Rare Diseases

https://doi.org/10.1186/s13023-026-04337-y

Article in Press

Six novel *SACS* mutations expand the autosomal recessive spastic ataxia of Charlevoix–Saguenay spectrum

Received: 26 November 2025

Accepted: 23 March 2026

Published online: 01 April 2026

Cite this article as: Ikenoshita S., Nomura T., Shimazaki H. *et al.* Six novel *SACS* mutations expand the autosomal recessive spastic ataxia of Charlevoix–Saguenay spectrum. *Orphanet J Rare Dis* (2026). https://doi.org/10.1186/s13023-026-04337-y

Susumu Ikenoshita, Toshiya Nomura, Haruo Shimazaki, Hiroyuki Uetani, Keiichi Nakahara, Takahiro Okazaki, Michie Imamura, Hironori Mizutani, Aoi Fudo, Yuya Jo, Soichiro Matsubara, Yujiro Higuchi, Toshinori Hirai, Hiroshi Takashima & Mitsuharu Ueda

Research article

Title: Six Novel *SACS* Mutations Expand the Autosomal Recessive Spastic Ataxia of Charlevoix–Saguenay Spectrum

Susumu Ikenoshita, MD, PhD[a*], Toshiya Nomura, MD, PhD[a], Haruo Shimazaki, MD, PhD[b,c], Hiroyuki Uetani, MD, PhD[d], Keiichi Nakahara, MD, PhD[a,e], Takahiro Okazaki, MD[f], Michie Imamura, MD[a], Hironori Mizutani, MD, PhD[a], Aoi Fudo, MD[a], Yuya Jo, MD[a], Soichiro Matsubara, MD, PhD[a], Yujiro Higuchi, MD, PhD[g], Toshinori Hirai, MD, PhD[d], Hiroshi Takashima, MD, PhD[g], Mitsuharu Ueda, MD, PhD[a,e]

[a]Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto 860-0811, Japan

[b]Faculty of Health & Medical Care, Saitama Medical University, Saitama 350-1241, Japan

[c]Department of Neurology, Jichi Medical University, Tochigi 329-0498, Japan

[d]Department of Diagnostic Radiology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto 860-0811, Japan

[e]Intractable Neurological Diseases Center, Kumamoto University Hospital, Kumamoto 860-0811, Japan

[f]Department of Neurology, Kumamoto General Hospital, Yatsushiro 866-8660, Japan

[g]Department of Neurology and Geriatrics, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, 890-8520, Japan

Correspondence to: Susumu Ikenoshita, MD, PhD

Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-0811, Japan

Tel: +81 96 373 5893, Fax: +81 96 373 5895

E-mail: s.ikenoshita1986@gmail.com

Abstract

Background: The clinical spectrum of autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) in Asian populations remains incompletely defined. We aimed to characterize the clinical, radiological, and genetic features of Japanese patients with ARSACS and to expand the mutational and phenotypic spectrum of this disorder.

Methods: We conducted a retrospective case series of patients diagnosed with ARSACS in our department between January 2016 and December 2023. Five patients from four families with biallelic *SACS* variants were identified.

Results: Genetic analysis revealed seven pathogenic *SACS* variants, of which six were novel. Clinical heterogeneity was notable, with age at onset ranging from 1 to 27 years. Four patients showed classical ARSACS-related neuroimaging findings, whereas one patient presented with a Charcot–

Marie–Tooth disease (CMT)-mimicking phenotype characterized by predominant peripheral neuropathy, mild cerebellar involvement, and absence of the classical pontocerebellar magnetic resonance imaging features.

Conclusions: The recognition of CMT-mimicking presentations supports considering ARSACS in the differential diagnosis of hereditary peripheral neuropathies, particularly in patients with additional cerebellar, pyramidal, or supportive neuroimaging features.

Keywords: Autosomal recessive spastic ataxia of Charlevoix–Saguenay, Charcot–Marie–Tooth disease, *SACS* variants, Hereditary neuropathy

Background

Autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) was first described in 1978 as a neurodegenerative disorder characterized by the triad of progressive cerebellar ataxia, lower limb spasticity, and sensorimotor peripheral neuropathy, typically manifesting in early childhood [1]. The identification of the *SACS* gene in 2000 has significantly advanced our understanding of this disorder, leading to an exponential increase in reported cases worldwide and revealing its pan-ethnic distribution [2]. Currently recognized as the second most prevalent early-onset autosomal recessive cerebellar ataxia globally [3], ARSACS remains significantly underdiagnosed because of its phenotypic heterogeneity.

Although ARSACS was first delineated in the Charlevoix–Saguenay region, subsequent studies have identified affected patients worldwide [4]. However, the clinical spectrum and diagnostic clues may be underrecognized in Asian populations, where patients present with variable combinations of spasticity, cerebellar signs, and peripheral neuropathy. Reports from East Asia have described both the “classic” ARSACS phenotype [5] and atypical presentations with predominant neuropathy, which may

initially be diagnosed as Charcot–Marie–Tooth disease (CMT) [6]. Systematic characterization of Asian cohorts remains limited; therefore, additional case series are needed to better define the phenotypic boundaries and expand the mutational spectrum of *SACS* in this region.

The diagnostic approach to ARSACS has traditionally relied on characteristic neuroimaging and ophthalmological findings. Typical magnetic resonance imaging (MRI) features include pontine linear hypointensity and superior cerebellar vermis atrophy, while ophthalmological findings include hypermyelinated retinal nerve fibers [7]. However, emerging evidence has expanded the phenotypic spectrum, encompassing cases without spasticity [8–10] and patients with cognitive impairment [11], thereby challenging the traditional diagnostic paradigm.

Since 2016, we have identified five patients with ARSACS from four families who demonstrate remarkable clinical heterogeneity, including adult-onset presentations and a neuropathy-predominant phenotype initially mimicking CMT. In this study, we aimed to characterize the clinical, neuroimaging, and genetic features of ARSACS to expand the phenotypic spectrum of this disorder and provide insights for the diagnostic recognition

of non-classical presentations.

Methods

We conducted a retrospective case series of patients diagnosed with ARSACS in our department between January 2016 and December 2023. Cases were identified through a review of medical records, genetic testing results, and neuroimaging findings obtained during routine clinical practice. At our institution, patients with suspected spinocerebellar degeneration are routinely admitted for comprehensive evaluation; therefore, cases were ascertained through a review of inpatient records. Patients were identified either through targeted *SACS* analysis when ARSACS was clinically suspected based on characteristic neurological and MRI features or through comprehensive genetic testing performed in patients with peripheral neuropathy [12]. We included genetically confirmed patients with biallelic *SACS* variants and sufficient clinical data for detailed analysis. Clinical information, including age at onset, presenting symptoms, disease course, neurological findings, nerve conduction study results, and ophthalmological evaluations, was collected retrospectively from medical records. Brain and

cervical spine MRI scans were reviewed for characteristic ARSACS-related findings, including cerebellar atrophy, pontine linear hypointensities, white matter abnormalities, brainstem changes, thalamic signal abnormalities, and spinal cord atrophy. Variants were interpreted according to the American College of Medical Genetics and Genomics guidelines using public databases, including ClinVar and gnomAD.

Results

Patient Summary

Between January 2016 and December 2023, we systematically evaluated 3,347 neurological inpatients admitted to our department, among whom five patients from four families were diagnosed with ARSACS based on biallelic *SACS* variants. This yielded hospital-based frequencies of 0.15% among all neurological admissions, 1.83% among patients with spinocerebellar degeneration (4/219), and 0.29% among those with peripheral neuropathy (1/348). Six variants were novel, expanding the mutational spectrum of ARSACS in Japan. Clinically, these cases showed a broad phenotypic spectrum ranging from classic ARSACS to neuropathy-predominant

presentations that could initially mimic CMT.

Genetic Findings

Biallelic *SACS* variants were identified in all five patients (Tables 1 and 2). The sibling cases from a consanguineous family harbored the same homozygous variant, whereas the remaining patients had compound heterozygous variants. Of the seven variants identified across the cases, six were novel. Detailed variant information and family segregation data are provided in Table 2 and Figure S1 in Additional file 1.

[Insert Table 1 here]

Table 2. Seven pathogenic sacsin/*SACS* variants in Japanese ARSACS cases

Sacsin protein variants	*SACS* gene variants	ClinVar accession no.	ClinVar classification	Allele frequency in gnomAD variants	References on clinical symptoms of variants

p.Arg88Ter	c.262C>T	VCV000559870.10	Pathogenic	2.48e-6 (4/1,611,046)	n/a
p.Ala720_Gly721insTyr	c.2159_2160insTTA	n/a	n/a	n/a	n/a
p.Lys1715Ter	c.5143A>T	VCV000917652.10	Pathogenic	8.71e-6 (14/1,607,636)	Ref 3
p.Arg2425Ter	c.7273C>T	VCV000370415.10	Pathogenic/likely pathogenic	1.18e-5 (19/1,613,212)	n/a
p.Glu3647Ter	c.10939G>T	VCV000458251.8	Pathogenic/likely pathogenic	2.48e-6 (4/1,613,752)	n/a
p.Pro3656Leu	c.10967C>T	n/a	n/a	6.20e-7 (1/1,613,888)	n/a
p.Phe4432Ter	c.13294_13295insAA	n/a	n/a	n/a	n/a

Six sacsin/*SACS* variants (p.Arg88Ter, p.Ala720_Gly721insTyr, p.Arg2425Ter, p.Glu3647Ter, p.Pro3656Leu, and p.Phe4432Ter) have not been previously described in the literature in individuals with ARSACS. Two of these variants (p.Ala720_Gly721insTyr and p.Phe4432Ter) are novel. The remaining variants are documented in public databases: three (p.Arg88Ter, p.Arg2425Ter, and p.Glu3647Ter) are present in ClinVar, and four (p.Arg88Ter, p.Arg2425Ter, p.Glu3647Ter, and p.Pro3656Leu) are found in gnomAD.

We used NG_012342.1 and NM_014363.6 as reference sequences.

n/a, not available; ARSACS, autosomal recessive spastic ataxia of Charlevoix–Saguenay.

Clinical Characteristics

Clinical presentations were heterogeneous. Age at onset ranged from childhood to adulthood, and gait disturbance was the predominant initial manifestation. Cerebellar ataxia and peripheral neuropathy were present in all patients, whereas cognitive involvement and pyramidal signs varied across cases. One patient exhibited a neuropathy-predominant phenotype with relatively mild cerebellar findings, initially resembling CMT.

Electrophysiological and Ophthalmological Findings

Nerve conduction studies consistently demonstrated sensorimotor neuropathy with mixed axonal and demyelinating features, predominantly affecting the lower limbs. Ophthalmological evaluation revealed ARSACS-associated retinal abnormalities in several patients, including increased visibility or thickening of the retinal nerve fiber layer (RNFL); however, no patient reported significant visual symptoms.

Neuroimaging Findings

Neuroimaging showed substantial heterogeneity. Four patients exhibited

typical ARSACS-related MRI features, including superior vermian atrophy, characteristic pontine signal abnormalities, and cervical spinal cord atrophy. In contrast, one patient lacked the typical pontocerebellar findings despite a confirmed molecular diagnosis and presented with a neuropathy-predominant phenotype that initially resembled CMT. Bilateral lateral thalamic T2 hyperintensities were observed in several patients, including the atypical case (Figure S2 in Additional file 1).

Discussion

In this retrospective case series, we identified five patients with ARSACS harboring seven *SACS* variants, six of which were novel. Notably, one patient presented with a neuropathy-predominant phenotype that initially resembled CMT and lacked classical MRI features, thereby expanding the recognized clinical spectrum and suggesting potential underdiagnosis of ARSACS among Japanese patients with hereditary neuropathies.

Our cases demonstrated notable phenotypic heterogeneity. Age at onset ranged from 1 to 27 years, with Case 5 representing a particularly atypical presentation, characterized by predominant peripheral neuropathy

with minimal cerebellar involvement and absence of the pathognomonic MRI features [7, 13]. This variability extends previous Japanese reports describing atypical presentations, including patients lacking spasticity [8] or prominent retinal myelinated fibers [14]. These findings suggest that ARSACS in Japanese patients may deviate substantially from classical diagnostic criteria.

The frequency of ARSACS among peripheral neuropathy cases in our cohort (0.29%) closely aligns with the 0.3% prevalence reported by Pi et al. among Korean families with suspected CMT [15]. However, an important distinction should be noted. Although the Korean patients were identified in a CMT cohort, they showed concurrent cerebellar ataxia and spasticity and retained characteristic brain MRI features, including superior vermian atrophy and pontine signal abnormalities [15]. In contrast, Case 5 in the present study lacked these classical imaging findings entirely. This difference suggests that reliance on traditional clinical and imaging criteria may contribute to underrecognition of ARSACS in Asian populations. Indeed, atypical ARSACS cases lacking overt spasticity, as well as cases initially diagnosed as CMT, have been reported from Japan and China, suggesting

that such phenotypes may be relatively frequent in East Asian populations (Table S1 in Additional file 1). Neuroimaging is a critical diagnostic tool in ARSACS [7, 13]. While four patients exhibited the pathognomonic combination of superior vermian atrophy and pontine linear hypointensities, Case 5 lacked these findings despite a confirmed genetic diagnosis. Notably, the “thalamic rim sign,” characterized by bilateral thalamic hyperintensities and reported in 100% of cases in previous series [16], was preserved even in Case 5, suggesting its value as an additional diagnostic marker [17] when classical features are absent. These findings highlight the need to reconsider diagnostic algorithms that rely heavily on pontine and vermian abnormalities.

ARSACS should not be regarded as a purely hereditary neuropathy but rather as a multisystem disorder characterized by variable combinations of cerebellar ataxia, pyramidal signs, and peripheral neuropathy. This overall neurological pattern, which has been well-described in previous series, may help distinguish ARSACS from CMT even when neuropathic features predominate. Nerve conduction studies in ARSACS may demonstrate demyelinating features, including slowed conduction velocities and prolonged distal latencies; however, these abnormalities are not necessarily

as severe or as uniform as those typically observed in classical CMT1, and some patients may even show mixed or predominantly axonal features. Therefore, demyelinating findings on nerve conduction studies should be interpreted within the broader clinical context, particularly when cerebellar, pyramidal, retinal, or characteristic neuroimaging features are present. Recent optical coherence tomography (OCT) studies have demonstrated that RNFL changes in ARSACS represent true axonal hypertrophy rather than hypermyelination [18–20], suggesting primary neuronal involvement. The dissociation between structural retinal abnormalities and preserved visual function observed in our patients supports RNFL thickening as a potential diagnostic biomarker, emphasizing the importance of OCT assessment even in asymptomatic patients.

The substantial diagnostic delay observed in our cases underscores persistent challenges in ARSACS recognition, which now encompasses presentations from classic early-onset forms to adult-onset cases with minimal cerebellar involvement [21]. Clinically, ARSACS should be considered in the differential diagnosis of both hereditary ataxias and peripheral neuropathies, regardless of age or classical neuroimaging

features. The combination of demyelinating neuropathy without nerve enlargement [22], thalamic hyperintensities, and RNFL thickening may facilitate diagnosis even when pontine and vermian abnormalities are absent.

Some limitations should be acknowledged. The cross-sectional design precludes assessment of disease progression, and the small sample size limits definitive genotype–phenotype correlations. Whether the classical and CMT-mimicking phenotypes reflect distinct pathogenic mechanisms remains unclear. Given that sacsin is a large multidomain protein involved in mitochondrial dynamics, cytoskeletal organization, and protein quality control, both phenotypes likely represent variable manifestations of sacsin dysfunction influenced by variant type, residual protein function, and genetic background. Future prospective studies incorporating functional analyses of novel variants and validation of emerging biomarkers in larger multicenter cohorts are needed.

Conclusions

Our identification of six novel *SACS* variants highlights the phenotypic heterogeneity in Japanese patients with ARSACS, including CMT-mimicking

presentations without characteristic MRI features. These findings expand both the genetic and clinical boundaries of ARSACS, supporting its consideration in the differential diagnosis of hereditary ataxias and peripheral neuropathies, particularly when suggestive clinical or neuroimaging features are present.

List of Abbreviations

ARSACS, autosomal recessive spastic ataxia of Charlevoix–Saguenay; CMAP, compound muscle action potential; CMT, Charcot–Marie–Tooth disease; MRI, magnetic resonance imaging; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; SNAP, sensory nerve action potential

Declarations

Ethics Approval and Consent to Participate

The Institutional Review Board of Kumamoto University approved this study (No. 496).

Written informed consent was obtained from all participants.

Consent for Publication

Written informed consent was obtained from all participants.

Availability of Data and Materials

Due to privacy and ethical restrictions, the datasets supporting the current study cannot be publicly shared. Data are available from the corresponding author upon reasonable request and with appropriate institutional approvals.

Competing Interests

Mitsuharu Ueda reports receiving research grants and lecturer fees from Alnylam and Pfizer outside of this study. Other authors report no competing interests.

Funding

This work was supported by JSPS KAKENHI [grant number JP25K19034, to SI].

Authors' Contributions

SI: conceptualization, data curation, funding acquisition, investigation, validation, and writing - original draft and editing.

TN: data curation, investigation, and writing - review & editing.

HS: data curation, investigation, methodology, and writing - review & editing.

HU: investigation and writing - review & editing.

KN: data curation, investigation, and writing - review & editing.

TO: data curation, investigation, and writing - review & editing.

MI: data curation, investigation, and writing - review & editing.

HM: data curation, investigation, and writing - review & editing.

AF: data curation, investigation, and writing - review & editing.

YJ: data curation, investigation, and writing - review & editing.

SM: data curation, investigation, and writing - review & editing.

YH: investigation, supervision, and writing - review & editing.

TH: investigation, supervision, and writing - review & editing.

HT: investigation, supervision, and writing - review & editing.

MU: conceptualization, data curation, funding acquisition, investigation, methodology, supervision, validation, visualization, and writing - original draft and review & editing.

Acknowledgements

The authors acknowledge the use of ChatGPT (OpenAI) for English language editing and manuscript formatting assistance. All scientific content, analyses, and conclusions are the sole work of the authors, who take full responsibility for the manuscript's integrity and accuracy.

Ethical Publication Statement

We have reviewed the journal’s guidelines on ethical publication and affirm that this report adheres to these standards.

References

[1] Bouchard JP, Barbeau A, Bouchard R, Bouchard RW. Autosomal recessive spastic ataxia of Charlevoix-Saguenay, Can. Can J Neurol Sci. 1978;5:61–9. https://doi.org/10.1017/S0317167100024793

[2] Engert JC, Bérubé P, Mercier J, Doré C, Lepage P, Ge B, et al. ARSACS, a spastic ataxia common in northeastern Québec, is caused by mutations in a new gene encoding an 11.5-kb ORF. Nat Genet. 2000;24:120–5. https://doi.org/10.1038/72769

[3] Vermeer S, Meijer RPP, Pijl BJ, Timmermans J, Cruysberg JRM, Bos MM, et al. ARSACS in the Dutch population: a frequent cause of early-onset cerebellar ataxia. Neurogenetics. 2008;9:207–14. https://doi.org/10.1007/s10048-008-0131-7

[4] Ouyang Y, Segers K, Bouquiaux O, Wang FC, Janin N, Andris C, et al. Novel SACS mutation in a Belgian family with sacsin-related ataxia. J Neurol Sci. 2008;264:73–6. https://doi.org/10.1016/j.jns.2007.07.022

[5] Kwon KY, Huh K, Eun BL, Yoo HW, Kamsteeg EJ, Scheffer H, et al. A probable Korean case of autosomal recessive spastic ataxia of Charlevoix-Saguenay. Can J Neurol Sci. 2015;42(4):271-3.

doi:10.1017/cjn.2015.38.

[6] Liu L, Tong X, Luo Y, Qu Q, Zhao M, Zhang L, et al. Autosomal recessive spastic ataxia of Charlevoix–Saguenay in a Chinese patient. J Neurol Sci. 2016;362:111–4. doi:10.1016/j.jns.2016.01.026.

[7] Martin MH, Bouchard JP, Sylvain M, St-Onge O, Truchon S. Autosomal recessive spastic ataxia of Charlevoix-Saguenay: A report of MR imaging in 5 patients. AJNR Am J Neuroradiol. 2007;28:1606–8. https://doi.org/10.3174/ajnr.A0603

[8] Shimazaki H, Takiyama Y, Sakoe K, Ando Y, Nakano I. A phenotype without spasticity in sacsin-related ataxia. Neurology. 2005;64:2129–31. https://doi.org/10.1212/01.WNL.0000166031.91514.B3

[9] Shimazaki H, Sakoe K, Niijima K, Nakano I, Takiyama Y. An unusual case of a spasticity-lacking phenotype with a novel SACS mutation. J Neurol Sci. 2007;255:87–9. https://doi.org/10.1016/j.jns.2007.02.002

[10] Chen Y, Cen Z, Zheng X, Chen S, Xie F, Luo W. Novel compound heterozygous SACS mutations in a case with a spasticity-lacking phenotype of sacsin-related ataxia. Neurol India. 2021;69:219–21. https://doi.org/10.4103/0028-3886.310115

[11] Ali Z, Klar J, Jameel M, Khan K, Fatima A, Raininko R, et al. Novel SACS mutations associated with intellectual disability, epilepsy and widespread supratentorial abnormalities. J Neurol Sci. 2016;371:105–11. https://doi.org/10.1016/j.jns.2016.10.032

[12] Ando M, Higuchi Y, Yuan JH, Yoshimura A, Dozono M, Hobara T, et al. Clinical phenotypic diversity of NOTCH2NLC-related disease in the largest case series of inherited peripheral neuropathy in Japan. J Neurol Neurosurg Psychiatry. 2023;94:622–30. https://doi.org/10.1136/jnnp-2022-330769

[13] Pedroso JL, Vale TC, França Junior MCF, Kauffman MA, Teive H, Barsottini OGP, et al. A diagnostic approach to spastic ataxia syndromes. Cerebellum. 2022;21:1073–84. https://doi.org/10.1007/s12311-021-01345-5

[14] Hara K, Onodera O, Endo M, Kondo H, Shiota H, Miki K, et al. Sacsin-related autosomal recessive ataxia without prominent retinal myelinated fibers in Japan. Mov Disord. 2005;20:380–2. https://doi.org/10.1002/mds.20315

[15] Pi BK, Chung YH, Kim HS, Nam SH, Lee AJ, Nam DE, et al. Compound

heterozygous mutations of SACS in a Korean cohort study of Charcot–Marie–Tooth disease concurrent cerebellar ataxia and spasticity. Int J Mol Sci. 2024;25:6378. https://doi.org/10.3390/ijms25126378

[16] Prodi E, Grisoli M, Panzeri M, Minati L, Fattori F, Erbetta A, et al. Supratentorial and pontine MRI abnormalities characterize recessive spastic ataxia of Charlevoix-Saguenay. A comprehensive study of an Italian series. Eur J Neurol. 2013;20:138–46. https://doi.org/10.1111/j.1468-1331.2012.03815.x

[17] Scaravilli A, Negroni D, Senatore C, Santorelli FM, Cocozza S. Current and future applications of brain magnetic resonance imaging in ARSACS. Cerebellum. 2025;24:91. https://doi.org/10.1007/s12311-025-01842-x

[18] Rezende Filho FM, Bremner F, Pedroso JL, de Andrade JBC, Marianelli BF, Lourenço CM, et al. Retinal architecture in autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS): insights into disease pathogenesis and biomarkers. Mov Disord. 2021;36:2027–35. https://doi.org/10.1002/mds.28612

[19] Suarez MK, Martin TJ, Ong SS. Thickened retinal nerve fiber layer without hypermyelination in autosomal recessive spastic ataxia of

Charlevoix-Saguenay. J Vitreoretin Dis. 2024;8:466–70. https://doi.org/10.1177/24741264241251582

[20] Garcia-Martin E, Pablo LE, Gazulla J, Polo V, Ferreras A, Larrosa JM. Retinal nerve fibre layer thickness in ARSACS: myelination or hypertrophy? Br J Ophthalmol. 2013;97:238–41. https://doi.org/10.1136/bjophthalmol-2012-302309

[21] Salem IH, Blais M, Zuluaga-Sánchez VM, Rouleau L, Becker EBE, Dupré N. ARSACS: clinical features, pathophysiology and iPS-derived models. Cerebellum. 2025;24:24. https://doi.org/10.1007/s12311-024-01777-9

[22] Kneer K, Straub S, Wittlinger J, Stahl JH, Winter N, Timmann D, et al. Neuropathy in ARSACS is demyelinating but without typical nerve enlargement in nerve ultrasound. J Neurol. 2024;271:2494–502. https://doi.org/10.1007/s00415-023-12159-2

Table 1. Clinical characteristics of patients with ARSACS

	Case 1	Case 2	Case 3	Case 4	Case 5
Preliminary diagnosis group	Spinocerebellar degeneration	Spinocerebellar degeneration	Spinocerebellar degeneration	Spinocerebellar degeneration	Hereditary peripheral neuropathy
Sex	M	F	M	F	M
Biallelic *SACS* variants	p.Glu3647Ter/	p.Glu3647Ter/	p.Arg88Ter/	p.Ala720_Gly721	p.Arg2425Ter/

	p.Glu3647Ter	p.Glu3647Ter	p.Lys1715Ter	insTyr/p.Phe4432Ter *	p.Pro3656Leu
Consanguineous marriage of the parents	+	+	−	−	−
Age of onset (years)	1	7	10	27	Early childhood
Initial symptoms	Gait instability	Gait instability	Gait instability	Gait instability	Impaired running ability
Age at initial presentation (years)	1	24	15	33	44
Age at diagnosis (years)	23	25	16	34	46
Intellectual disability	+	±	+	−	−
Cerebellar ataxia	+	+	+	+	±
Nystagmus	+	+	+	+	−
Dysarthria	+	+	−	−	−
Gait disturbance	+	+	+	+	±
Patellar hyperreflexia	+	+	±	+	+
Babinski sign	+	+	±	+	+
Distal hand atrophy	+	−	+	+	+
Pes cavus	+	+	+	+	+
Nerve conduction studies at diagnosis					
Axonal-demyelinating sensorimotor neuropathy with lower limb predominance	+	+	+	+	+
Median CMAP amplitude (mV)	5.7	2.2	4.4	10.6	5.2
Median MCV (m/s)	49.0	58.9	45.5	38.0	46.1
Median F latency (ms)	40.3	36.4	30.3	30.5	34.1
Median SNAP amplitude (μV)	Absent	Absent	2.3	Absent	18.4
Median SCV (m/s)	Absent	Absent	32.1	Absent	45.5
Peroneal CMAP amplitude (mV)	Absent	Absent	0.4	0.36	Absent
Peroneal MCV (m/s)	Absent	Absent	62.0	23.1	Absent
Sural SNAP amplitude (μV)	Absent	Absent	Absent	Absent	1.2
Sural SCV (m/s)	Absent	Absent	Absent	Absent	27.0
Ophthalmological findings					
Increased visibility of the retinal nerve fiber layer	+	−	+	−	−
Thickening of retinal nerve fibers	+	n/a	+	+	n/a

CNS MRI findings					
Superior cerebellar vermian atrophy	+	+	+	+	−
T2 hypointensities at the ventral pons with lateral hyperintense stripes	+	+	+	+	−
Bilateral symmetrical T2 hyperintensities in the lateral thalamus	−	+	+	+	+
Cervical spinal cord atrophy	+	+	+	+	±

Cases 1 and 2 involved siblings.

* Segregation analysis not available.

F, Female; M, male; NCS, nerve conduction study; RNF, retinal nerve fibers; pRNFL, peripapillary retinal nerve fiber layer; n/a, not available; ARSACS, autosomal recessive spastic ataxia of Charlevoix–Saguenay; CMAP, compound muscle action potential; MCV, motor conduction velocity; SNAP, sensory nerve action potential; SCV, sensory conduction velocity; CNS, central nervous system; MRI, magnetic resonance imaging.

Additional Files

File name: Additional file 1

File format: .docx

Title of data: Figure S1. Pedigrees and ARSACS gene mutations in five Japanese cases from four families. Figure S2. Illustrative comparison of classical and atypical brain MRI findings in two patients with ARSACS. Table S1. Atypical ARSACS cases in East Asia

Description of data: Additional file 1 contains supplementary figures and a table, including Figure S1 showing the pedigrees and genetic findings of five Japanese cases from four families, Figure S2 illustrating representative MRI findings of classical and atypical ARSACS phenotypes, and Table S1 summarizing previously reported atypical ARSACS cases in East Asia.