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LETTER TO THE EDITOR

Sacsin-Related Spastic Ataxia Caused by a Novel Missense Mutation p.Arg272His in a Patient from Sicily, Southern Italy

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Introduction

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a neurodegenerative disorder characterized by early-onset spastic ataxia, dysarthria, nystagmus, distal muscle wasting, peripheral neuropathy, finger and foot deformities, and hypermyelination of retinal nerve fibers [1]. Brain imaging often reveals cerebellar hemispheres and superior vermis atrophy, spinal cord atrophy, and linear hypointensities of the pons [2]. The gene *SACS* responsible for the ARSACS was mapped to chromosome 13q11 [3] and consists in one gigantic and eight smaller upstream exons [4]. We report a novel *SACS* mutation in a Sicilian family with ARSACS phenotype.

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Methods

Clinical Study

A woman, aged 36 years, was referred to our hospital for evaluation of ataxia. She was born from non-consanguineous parents and early motor milestones were normal. Eleven members of the family were studied. Informed consent was obtained from all family members involved.

Molecular Study

Genomic DNA of the patient and relatives was extracted from blood lymphocytes using standard procedure. We performed sequence analysis of the transcript of the *SACS* gene (NM_014363.4) that comprises nine exons. The nine coding exons, including the gigantic exon described previously, as well as flanking intronic sequences of the *SACS* gene were polymerase chain reaction (PCR)-amplified from genomic DNA by using 37 primer pairs. Primer sequences and amplification parameters are available on request. Purified PCR products (Wizard SV Gel and PCR Clean-Up System, Promega Corporation 2800 Woods Hollow Road Madison, WI 53711-5399 USA) were directly sequenced on an ABI3130 automated sequencer (Applied Biosystems, Foster City, CA, USA). In addition, mutation analysis was performed in patient's parents and siblings to confirm the

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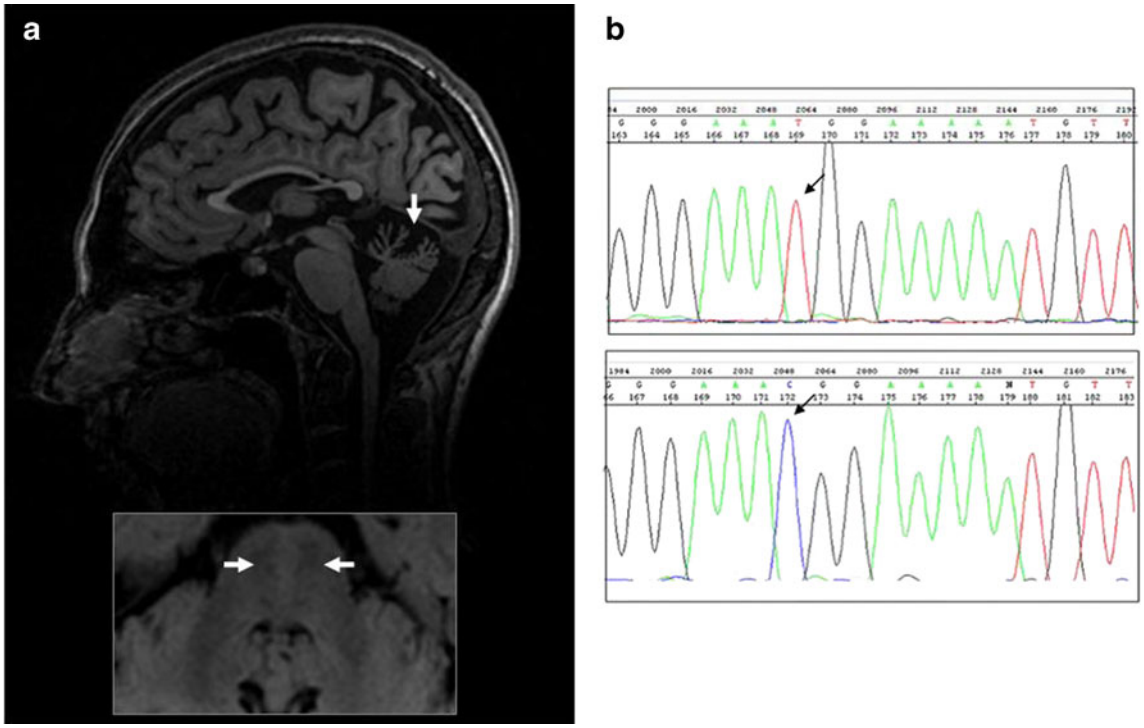

Fig. 1 **a** Sagittal T1-weighted (*top*) and axial T2-weighted FLAIR (*bottom*) MRI showing, respectively, upper cerebellar vermis atrophy and mild hypointensities in the pons—see *white arrows*; **b** electropherograms of the novel homozygous missense mutation (c.815G>A) in the patient (*top*) and wild-type sequence (*bottom*)—see *black arrows*

segregation of the mutation with the disease phenotype. A total of 200 control chromosomes were sequenced.

Results

Clinical Findings

The patient was a 36-year-old woman with clumsy gait since infancy. Two years ago, she presented a progressive worsening of her gait problems with imbalance and frequent falls. Neurological examination showed spastic ataxic gait, brisk tendon reflexes in all four limbs with left Babinski sign, bilateral ankles clonus, low gain pursuit, gaze-evoked horizontal nystagmus, and mild dysmetria in all four limbs. Speech was mildly slurred. The patient presented also *pes cavus* and hyperlordosis of the lumbar spine. Peripheral nerve conduction study demonstrated mixed sensory–motor neuropathy, mainly demyelinating. Visual-evoked potentials showed increased latencies of P100 components bilaterally. Fundoscopy did not reveal hypermyelinated retinal fibers. Brain MRI revealed upper cerebellar vermis atrophy and mild hypointensities in the pons (Fig. 1a)

Molecular Findings

Genetic analysis for Friedreich ataxia was negative. A novel homozygous missense mutation in the *SACS* gene (G-to-A transition at c.815) was identified in the patient (Fig. 1b). c.815G>A results in the substitution of arginine with histidine at amino acid residue 272 (p.R272H). This substitution was present in heterozygosis in both unaffected parents (as in one unaffected sibling and in two unaffected relatives) but was absent in one healthy sibling. The novel c.815G>A putative mutation was not detected among 200 control chromosomes. The p.R272 residue in SACS is conserved in different species.

Discussion

SACS gene mutations have been described in different worldwide regions [5]. Our patient clinical features and MRI findings are very similar to those found in Quebec patients except for the retinal hypermyelination, confirming that this sign is rare outside Quebec [5, 6]. Most of the *SACS* mutations identified worldwide have been located in the gigantic exon 9. Only a few mutations were identified upstream from this exon, predominantly in exon 7. Clinical characteristics associated with the described exon 7-located *SACS* mutations are shown in Table 1. As in our patient, the core clinical features of patients with mutations in exon 7 of *SACS* seem to be identical to those of patients with mutation in exon 9 [7]. Despite the clinical presentation is similar in the majority of patients, some reports have revealed that

Table 1 Clinical characteristics associated with described exon 7-located *SACS* mutations

	Ouyang et al. 2006 [4]	Takado et al. 2007 [7]	Vermeer et al. 2008 [11]	Guernsey et al. 2010 [12]	Baets et al. 2010 [8]	Prodi et al. 2012 [10]	Our case 2012
Mutation	W395fsX12 V687fsX26	L308F	R321X W492X	R272C	L556P	R276C R321X	R272H
Type of mutation	Frameshift	Missense	Nonsense	Missense	Missense	Missense/nonsense	Missense
Origin	Japan	Japan	Netherlands	Maritime Canada	Marocco (Belgium)	Italy	Italy
Consanguineous parents	No	Yes	No	–	Yes	–	No
Sex	Woman	Man/woman	Woman	–	–	–	Woman
Age at onset	Childhood	Childhood/early childhood	Early childhood	Childhood/adulthood	Childhood	Childhood/early childhood	Childhood
Symptoms at onset	Gait disturbance	Gait disturbance/ mental retardation	–	–	Distal weakness of lower limbs/ foot deformities	Gait instability and frequent falls	Gait disturbance
Spasticity	Yes	Yes	Yes	Yes/no	Yes	Yes	Yes
Dysarthria	Yes	Yes	–	Yes	Yes	–	Yes
Ocular movements abnormalities	Altered pursuit	Nystagmus	–	Nystagmus	Nystagmus	–	Nystagmus
Pes cavus	Yes	Yes	–	Yes	Yes	Yes	Yes
Myelinated retinal nerve fibers	No	No	–	–	No	–	No
Neuropathy	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cognitive impairment	–	No/yes	–	–	Yes	–	No
MRI alterations	Cerebellar vermis atrophy	Cerebellar vermis and spinal cord atrophy	Cerebellar vermis atrophy	–	Cerebellar atrophy	–	Cerebellar vermis atrophy and linear pons hypointensities

ARSACS may show also atypical features such as a spasticity-lacking phenotype or a delayed-onset form [8, 9]. Until the present study, other mutations have been reported in Italy [10]. p.R272H represents a novel Italian mutation located upstream of the giant exon of the *SACS* gene. The missense mutation we found was not detected among 200 control chromosomes. Although it is in a well-conserved region of the protein, no functional domain is defined for this region.

Conflict of interest Authors have nothing to report.

References

1. Bouchard JP, Barbeau A, Bouchard R, Bouchard RW. Autosomal recessive spastic ataxia of Charlevoix-Saguenay. Can J Neurol Sci. 1978;5:61–9.
2. 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.
3. 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.
4. Ouyang Y, Takiyama Y, Sakoe K, Shimazaki H, Ogawa T, Nagano S, et al. Sacsin-related ataxia (ARSACS): expanding the genotype upstream from the gigantic exon. Neurology. 2006;66:1103–4.
5. Criscuolo C, Saccà F, De Michele G, Mancini P, Combarros O, Infante J, et al. Novel mutation of *SACS* gene in a Spanish family with autosomal recessive spastic ataxia. Mov Disord. 2005;20:1358–61.
6. Grieco GS, Malandrini A, Comanducci G, Leuzzi V, Valoppi M, Tessa A, et al. Novel *SACS* mutations in autosomal recessive spastic ataxia of Charlevoix-Saguenay type. Neurology. 2004;62:103–6.
7. Takado Y, Hara K, Shimohata T, Tokiguchi S, Onodera O, Nishizawa M. New mutation in the non-gigantic exon of *SACS* in Japanese siblings. Mov Disord. 2007;22:748–9.
8. Baets J, Deconinck T, Smets K, Goossens D, Van den Bergh P, Dahan K, et al. Mutations in *SACS* cause atypical and late-onset forms of ARSACS. Neurology. 2010;75:1181–8.
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(1–2):87–9.
10. 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(1):138–46.
11. Vermeer S, Meijer RP, Pijl BJ, Timmermans J, Cruysberg JR, Bos MM, et al. ARSACS in the Dutch population: a frequent cause of early-onset cerebellar ataxia. Neurogenetics. 2008;9:207–14.
12. Guernsey DL, Dubé MP, Jiang H, Asselin G, Blowers S, Evans S, et al. Novel mutations in the sacsin gene in ataxia patients from Maritime Canada. J Neurol Sci. 2010;288:79–87.