Original Article

Complicated paroxysmal kinesigenic dyskinesia associated with *SACS* mutations

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Background: Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is caused by pathogenic variants in the SACS gene and is characterized by ataxia, peripheral neuropathy, pyramidal impairment and episodic conditions such as epilepsy. Paroxysmal kinesigenic dyskinesia (PKD) had not been previously described in ARSACS.

Methods: We analyzed clinical manifestations and performed whole-exome sequencing (WES) in two independent patients with ARSACS and PKD. Both patients' parents were unaffected. Genetic data were filtered for potential pathogenic variants, searching for de novo mutations suggestive of a dominant disease model or homozygous and compound heterozygous variants of a recessive model. Potential mutations that existed in both patients were generated and subjected to Sanger sequencing. The WES results of 163 PKD patients without additional symptoms from previous experiments were also reviewed.

Results: Novel compound heterozygous mutations in the SACS gene were identified in Patient 1 (p.P3007S and p.H3392fs), and a novel homozygous truncating mutation (p.W1376X) was identified in Patient 2. In both patients, each mutant allele was inherited from one of his or her unaffected parents. All 3 mutations were absent in 196 ethnic-matched control chromosomes or in data from the 1000 Genomes Project. No pathogenic variants associated with paroxysmal diseases, especially PKD and episodic ataxia, were identified. In PKD patients without additional symptoms, no homozygous or compound heterozygous variants in the SACS gene were detected.

Conclusions: This study expands the clinical phenotype of ARSACS and suggests the inclusion of *SACS* screening in patients with PKD plus ARSACS.

Keywords: Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS); paroxysmal kinesigenic dyskinesia (PKD); mutation; *SACS*

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Introduction

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS, OMIM #270550) is an early-onset progressive disorder that mainly presents with spinocerebellar ataxia, upper motor neuron dysfunction, and distal sensorimotor and peripheral neuropathy (1). ARSACS is caused by pathogenic variants in *SACS* (2). Paroxysmal kinesigenic dyskinesia (PKD, OMIM #128200) is characterized by recurrent and brief attacks of dystonia and choreoathetosis lasting no more than 1 minute, triggered by sudden movements (3). Mutations in *PRRT2* and *SCN8A* are associated with PKD (4,5). We describe here two independent cases bearing *SACS* mutations presented with ARSACS and PKD, which expands the clinical phenotype associated with *SACS* mutations to include PKD.

Methods

The study was approved by the ethical review board of Peking Union Medical College Hospital. Both families provided written informed consent for clinical-genetic correlation studies.

Genetic analysis

Genomic DNA was extracted from peripheral blood leukocytes using a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA) according to standard protocols. Mutations in *PRRT2* were excluded by Sanger sequencing, and WES was then performed on the two patients. Exonic regions were captured and enriched using an Agilent SureSelect Human All Exon 50 Mb kit (Agilent, Santa Clara, CA, USA). The captured fragments were purified and sequenced on a Hiseq2000 platform (Illumina, San Diego, CA, USA) using 90-bp paired-end reads. The sequence was aligned to the human reference genome (UCSC hg19) using a Burrows-Wheeler Aligner (6). The aligned sequence files were reformatted using SAMtools (7). Subsequent annotation was performed using SeattleSeq Annotation 138 (http://snp.gs.washington.edu/SeattleSeqAnnotation138/), SIFT (http://sift.jcvi.org/), and PolyPhen2 (http://genetics.bwh.harvard.edu/pph2/). Variant frequencies were initially determined in dbSNP, the 1000 Genomes Project, and the NHLBI Exome Sequencing Project version ESP6500 exome variant server [http://evs.gs.washington.edu/EVS/ (1 Dec 2013)] to remove common single nucleotide polymorphisms (SNPs). Only nonsynonymous, splicing and frameshift variants with minor allele frequency (MAF) <0.5% or that were absent in population databases were selected for further assessment. *De novo* mutations suggestive of a dominant disease model or homozygous and compound heterozygous variants of a recessive model were identified and subjected to Sanger sequencing. Genes that may potentially be related to paroxysmal dystonic symptoms were carefully excluded. The WES results of 163 PKD patients without additional symptoms (patients from a previous experiment (8) were also reviewed.

Results

Case reports

Patient 1 is a 14-year-old male. He developed unsteady gait and poor coordination at approximately 2 years old. Weakness and numbness were also reported, and all the symptoms progressively worsened. At the age of eight, he experienced recurrent and brief attacks of dystonia in unilateral or bilateral limbs triggered by sudden movements, stress or anxiety. The attacks lasted less than 10 seconds and were completely relieved by carbamazepine (CBZ) (200 mg/day). He reported no seizure attacks. Upon physical examination, he had jerky ocular pursuits, saccade dysmetria, mild distal weakness, pyramidal signs, cerebellar ataxia and high arch (*Figure 1A*).

Patient 2 is a 12-year-old female. She had strangling steps from 1.5 years on that worsened as ataxia became prominent. Mild learning difficulties were also noticed after she had entered primary school. When she was 10 years old, she began to experience episodes of unilateral or bilateral dystonia, causing instant falls with consciousness reserved. These attacks may be triggered by sudden movements or stress. Each attack lasted approximately 5 seconds and was favorably controlled by low-dose CBZ (100 mg/day). Her parents observed no seizure events. Physical examination showed dysarthria, counting deficits, saccade dysmetria, distal weakness, pyramidal signs, and cerebellar ataxia.

For both patients, routine serum tests, blood lactate concentration, ceruloplasmin, organic acids and amino acids were performed and were all within normal ranges. Neurophysiological examination revealed large-fiber sensorimotor axonal-demyelinating neuropathy. Brain magnetic resonance imaging revealed generalized atrophy, most markedly affecting the cerebellum. Typical cerebellar and pontine changes manifesting as hypointensities in T2-weighted images associated with ARSACS (9) were

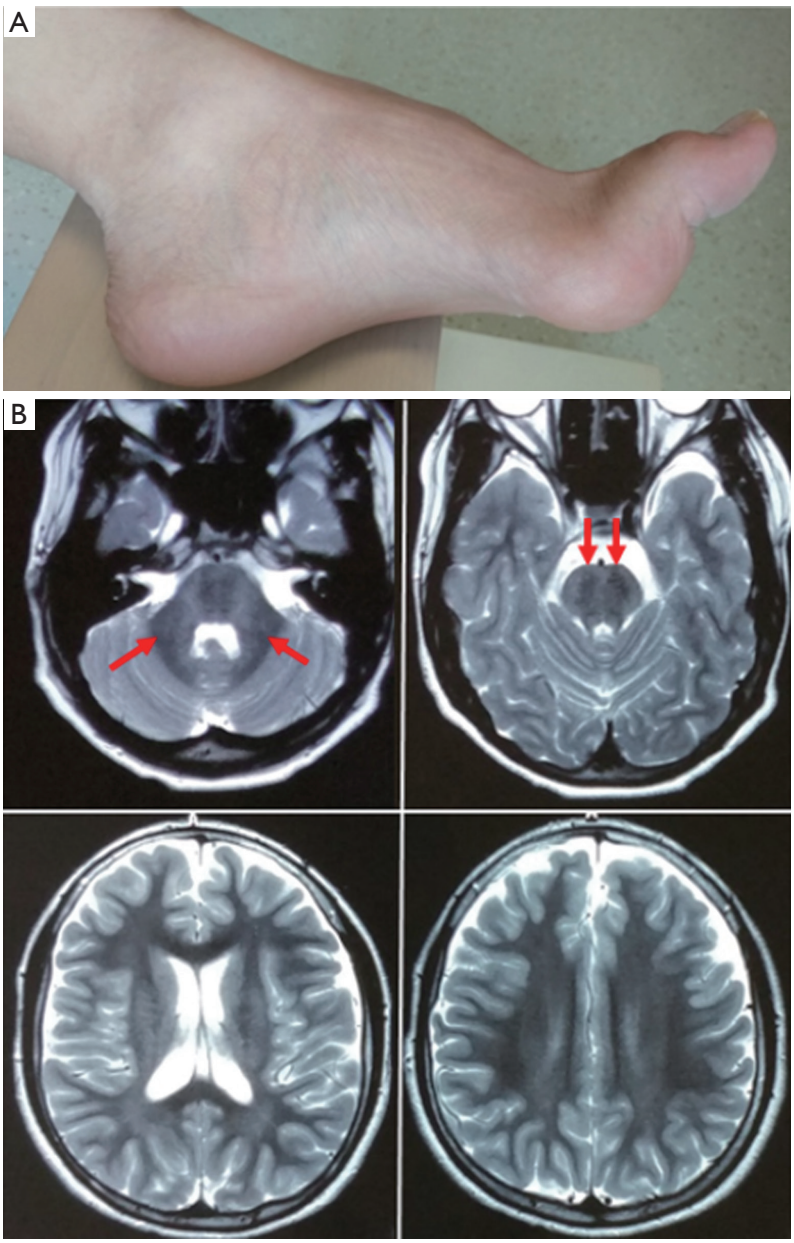

Figure 1 Clinical investigation of a patient with autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) and paroxysmal kinesigenic dyskinesia (PKD). (A) The abnormal high arch of Patient 1; (B) brain imaging of Patient 1 showing generalized atrophy, most markedly affecting the cerebellum, and typical hypointensities of the cerebellar peduncles and pons in T2-weighted images (arrows).

observed in our patients (see *Figure 1B*). For both patients, electroencephalography (EEG) detected no epileptic discharges. Increased amounts of slow waves in the bilateral frontal lobe were detected in Patient 2. Neurophysiological examination showed sensorimotor axonal polyneuropathy for both patients.

Genetic tests for spinocerebellar ataxias 1, 2, 3, 6, 7, 8, 10, 12 and 17, Friedreich ataxia, and dentatorubral-pallidoluysian atrophy (DRPLA) were negative, and patients' DNA samples were subsequently subjected to whole-exome sequencing (WES). After the *SACS* mutations were identified, both patients were treated with energy supplements primarily to treat mitochondrial deficits. During the 4-year follow up, Patient 1 deteriorated slowly

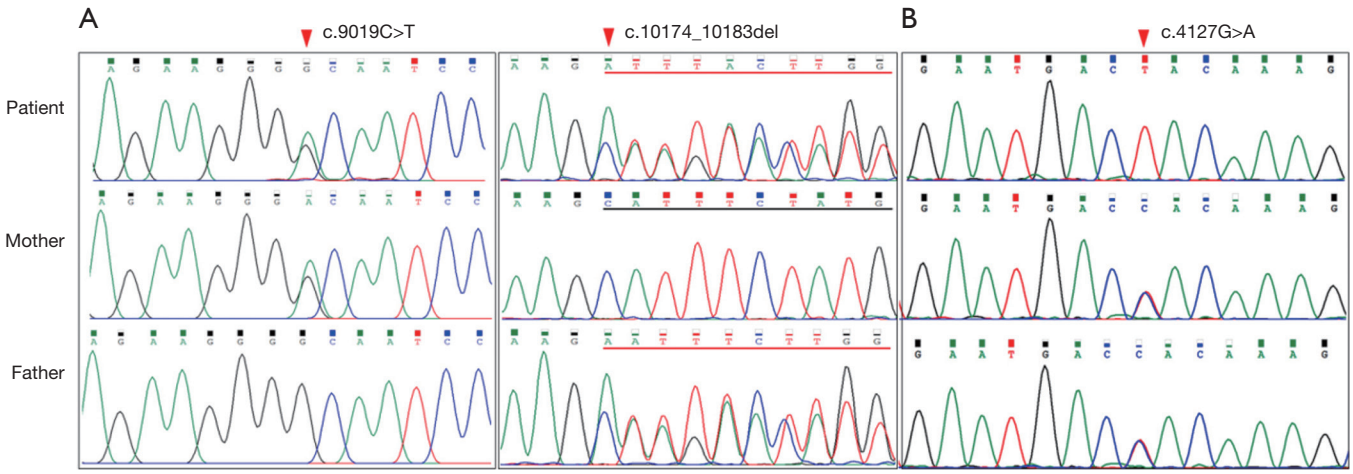

Figure 2 Sanger sequencing of mutations in two patients with autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) and paroxysmal kinesigenic dyskinesia (PKD). (A) The compound heterozygous mutations (c.9019C>T, and c.10174_10183del) of Patient 1, each inherited from his parents; the c.9019C>T was held by his mother and the c.10174_10183del by his father. (B) The homozygous mutation (c.4127G>A) detected in Patient 2, which presented as heterozygosis in her parents. The red arrowheads indicate mutation loci.

in his motor skills, with mild distant limb numbness and weakness. However, other than that, his ataxia was relatively stable, and his PKD was controlled satisfactorily. Patient 2 was lost to follow-up.

None of the rare variants with a minor allele frequency less than 0.5% were identified in the known genes associated with PKD. As other paroxysmal dystonic disorders cannot be completely excluded, genes potentially associated with the current symptoms were also carefully examined. These included the genes of *ADCY5*, *ATP1A3*, *GCH1*, *KCNMA1*, *PARK2*, *MR1*, *SLC2A1*, *KCNA1*, *CACNB4*, *CACNA1A*, *CACNB4*, *SLC1A3*, *KCNQ2* and *SLC1A3*. One variant was found in *CACNA1A* (c.1337T>C) in Patient 2. It was inherited from her mother who had no history of episodic symptoms and showed no signs of ataxia upon physical examination. The *CACNA1A* variant was thus considered less likely to be the causal gene. All potential pathogenic variants of the two patients are listed in *Tables S1* and *S2*.

The *SACS* gene (NM_014363.5) was the only gene associated with the existing phenotype in concordance with the symptoms of Patient 1 and Patient 2 and shared by them. Novel compound heterozygous or homozygous variants were revealed when comparing candidate genes and were confirmed by Sanger sequencing in both patients. Patient 1 holds one missense and one frameshift variant in the *SACS* gene (c.9019C>T, p.P3007S and c.10174_10183del, p.H3392fs) (*Figure 2A*). The homozygous variant presented in Patient 2 (c.4127G>A, p.W1376X) (*Figure 2B*) should be deleterious and would possibly cause truncation of the SACS protein. In both patients, each mutant allele was inherited from one of his or her unaffected parents. All 3 mutations had not been reported before and were absent in 196 ethnic-matched control chromosomes or in data from the 1000 Genomes Project. They were thus assigned as likely pathogenic.

In searching for additional genes that may have caused the PKD symptoms of our patients, we also reviewed the WES results of patients with pure PKD symptoms for *SACS* variations. There were 34 patients who carried heterozygous variants out of 163 PKD patients. However, 17 of these variants were documented in public databases with a reported allele frequency of over 0.3%. Three patients carried a pathological *PRRT2* mutation simultaneously. No homozygous or compound heterozygous variants in the *SACS* gene were detected in these patients.

Discussion

ARSACS is a neurodegenerative disease resulting from mutations in *SACS*. Over 170 mutations with diverse phenotypes have been reported worldwide and are thought to cause loss of function of sacsin (1). The typical ARSACS phenotype consists of a childhood-onset triad of cerebellar ataxia, peripheral neuropathy, and pyramidal tract signs. Reports describe patients with atypical features in addition to ataxia and peripheral neuropathy, which include delayed

onset ataxia, non-ataxic spastic paraplegia, mild pyramidal signs, cognitive decline, and widespread supratentorial abnormalities (10-13). Seizures including progressive myoclonus epilepsies were also reported (11,14-16). PKD, however, has never been documented in ARSACS before. Commonly, PKD is simple and pure in phenotype in addition to its association with epilepsy and migraines. Herein, we described 2 unrelated patients bearing mutations in *SACS* who presented with ARSACS and PKD. These findings may indicate that *SACS* is highly likely the causal gene of the combined syndrome and should be put to future biological validation.

The *SACS* gene encodes sacsin, a protein located on the mitochondrial surface. Sacs knockout ($Sacs^{-/-}$) mice displayed an abnormal gait with progressive motor dysfunction. Clinical features were accompanied by an early onset, progressive loss of cerebellar Purkinje cells followed by spinal motor neuron loss and peripheral nerve dysfunctions highly reminiscent of ARSACS (17). Remarkable bioenergetic damage in ARSACS cells is indicated by reduced basal, adenosine triphosphate (ATP)-linked and maximal mitochondrial respiration rates and by reduced respiratory chain activities and mitochondrial ATP synthesis (18). These findings show that defects in mitochondrial dynamics are the underlying pathophysiological basis of ARSACS (19). Supplementation of mitochondrial energy may thus be the current plan for symptom rescue, and it can be expected that in the near future, gene therapy may possibly be the cure.

In conclusion, we identified mutations in the *SACS* gene in two independent patients with ARSACS and PKD. Patients with *SACS* mutations may manifest a PKD phenotype under the background of ARSACS. This is different from PKD patients with mutations in *PRRT2* or other mutant genes, such as *SCN8A*, who show relatively pure paroxysmal dystonic deficits.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the ethical review board of Peking Union Medical College Hospital (No. JS-1049 of PUMCH). Both families provided written informed consent for clinical-genetic correlation studies.

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Supplementary

Table S1 Variants identified by whole-exome sequencing of Patient 1

Gene	#MIM	Position	cDNA changes	Protein changes	Type
PPOX	NM_000309	exon9	c.873delC	p.L291fs	het
ATR	NM_001184	exon10	c.2320dupA	p.I774fs	het
DUX4L4	NM_001177376	exon1	c.848_857del	p.V283fs	het
SPRY4	NM_001127496	exon2	c.227delC	p.P76fs	het
BMS1	NM_014753	exon7	c.880delA	p.K294fs	het
KIF21A	NM_001173463	exon26	c.3643dupA	p.I1215fs	het
CEP290	NM_025114	exon17	c.1666dupA	p.I556fs	het
SACS	**NM_001278055**	**exon8**	**c.10174_10183del**	**p.H3392fs**	**het**
DUOX2	NM_014080	exon6	c.605_621del	p.Q202fs	het
STAT5B	NM_012448	exon9	c.1102delC	p.Q368fs	het
SBF1	NM_002972	exon33	c.4469delT	p.F1490fs	het
PHKA1	NM_001172436	exon29	c.3244delA	p.I1082X	het
ALG6	NM_013339	exon15	c.1414G>C	p.V472L	het
PXDN	NM_012293	exon1	c.131G>A	p.R44H	het
IFT172	NM_015662	exon15	c.1513C>T	p.R505W	het
SCN9A	NM_002977	exon17	c.3112G>A	p.G1038S	het
LRP2	NM_004525	exon62	c.11684G>A	p.R3895H	het
TTN	NM_001256850	exon3	c.271A>G	p.S91G	het
HTR2B	NM_000867	exon2	c.244G>A	p.E82K	het
FAT4	NM_001291285	exon9	c.10124T>C	p.V3375A	het
DUX4L4	NM_001177376	exon1	c.779C>T	p.P260L	het
DUX4L4	NM_001177376	exon1	c.782C>T	p.P261L	het
TNXB	NM_019105	exon28	c.9476C>G	p.P3159R	het
EPM2A	NM_001018041	exon1	c.77G>A	p.R26Q	het
KCNH2	NM_172057	exon10	c.2132+3G>T	splicing	het
KMT2C	NM_170606	exon43	c.10214G>A	p.R3405Q	het
SLC52A2	NM_001253815	exon3	c.547C>A	p.P183T	het
ABCA1	NM_005502	exon37	c.5002G>A	p.V1668I	het
GSN	NM_198252	exon10	c.1191+3A>G	splicing	het
PAX6	NM_001127612	exon8	c.358-4G>A	splicing	het
GPD1	NM_001257199	exon6	c.742C>T	p.R248W	het
SACS	**NM_001278055**	**exon8**	**c.9019C>T**	**p.P3007S**	**het**
CASC5	NM_144508	exon10	c.590A>G	p.K197R	het
KIF23	NM_001281301	exon13	c.1117T>C	p.C373R	het
SOX18	NM_018419	exon2	c.799G>A	p.A267T	het
FTCD	NM_006657	exon9	c.1060C>T	p.P354S	het
EBP	NM_006579	exon5	c.690C>A	p.N230K	het
CACNA1F	NM_001256789	exon2	c.247C>T	p.R83W	hom
SRPX2	NM_014467	exon4	c.257G>A	p.R86H	hom
SH2D1A	NM_001114937	exon2	c.170C>G	p.S57C	hom

Table S2 Variants identified by whole-exome sequencing of Patient 2

Gene	#MIM	Position	cDNA changes	Protein changes	Type
DUX4L4	NM_001177376	exon1	c.848_857del	p.V283fs	het
ABCB4	NM_000443	exon10	c.1015dupT	p.S339fs	het
VCP	NM_007126	exon14	c.1847dupA	p.N616fs	het
DUX4L2	NM_001127386	exon1	c.571delC	p.P191fs	het
HBZ	NM_005332	exon2	c.155_156insGTCC	p.G52fs	het
FANCA	NM_000135	exon34	c.3378dupG	p.T1127fs	het
IGLL1	NM_020070	exon1	c.26delG	p.G9fs	het
ATP13A2	NM_022089	exon13	c.1195+5G>A	splicing	het
HSPG2	NM_001291860	exon12	c.1417G>T	p.D473Y	het
NID1	NM_002508	exon20	c.3730A>G	p.I1244V	het
COX20	NM_198076	exon2	c.62T>C	p.F21S	het
DCTN1	NM_001135041	exon11	c.1429C>T	p.L477F	het
WNT10A	NM_025216	exon4	c.926A>G	p.Q309R	het
SCN5A	NM_000335	exon12	c.1579G>A	p.G527R	het
DUX4L4	NM_001177376	exon1	c.899C>T	p.A300V	het
NSUN2	NM_017755	exon13	c.1323+1G>A	splicing	het
MAP3K1	NM_005921	exon1	c.233T>C	p.L78P	het
SYNPO	NM_007286	exon3	c.2321C>T	p.S774L	het
PEX6	NM_000287	exon1	c.839A>T	p.N280I	het
MAD1L1	NM_001013836	exon13	c.1306C>T	p.R436W	het
DNAH11	NM_001277115	exon34	c.5825G>C	p.G1942A	het
NPC1L1	NM_001101648	exon10	c.2618A>G	p.Q873R	het
ITGA8	NM_001291494	exon1	c.127G>A	p.V43M	het
CUBN	NM_001081	exon24	c.3371A>G	p.Y1124C	het
PYGM	NM_001164716	exon1	c.101G>A	p.R34Q	het
ATN1	NM_001007026	exon5	c.1346G>A	p.G449D	het
KERA	NM_007035	exon2	c.304C>A	p.L102I	het
TRPV4	NM_001177433	exon13	c.2162G>A	p.R721H	het
SACS	**NM_001278055**	**exon8**	**c.4127G>A**	**p.W1376X**	**hom**
SLC10A2	NM_000452	exon2	c.401C>T	p.T134I	het
PKD1	NM_000296	exon15	c.6285C>A	p.D2095E	het
ATP2A1	NM_001286075	exon12	c.1303C>T	p.R435C	het
SRCAP	NM_006662	exon4	c.73A>C	p.T25P	het
MYO15A	NM_016239	exon32	c.6893G>A	p.R2298Q	het
LAMA3	NM_001127717	exon27	c.3298G>A	p.V1100I	het
LAMA3	NM_001127718	exon34	c.4520A>G	p.H1507R	het
DSC2	NM_004949	exon3	c.251C>A	p.T84N	het
CACNA1A	NM_001127221	exon10	c.1337T>C	p.I446T	het
FUT1	NM_000148	exon4	c.790G>C	p.G264R	het
CRYAA	NM_000394	exon1	c.92T>C	p.L31P	het
BRWD3	NM_153252	exon35	c.3998C>A	p.S1333Y	het
ATP2B3	NM_001001344	exon8	c.1220C>T	p.T407M	het