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CLINICAL REPORT

A novel *SYNJ1* homozygous variant causing developmental and epileptic encephalopathy in an Afro-Caribbean individual

Mary Maj[1] | **Christie L. Taylor**[2] | **Kevin Landau**[1] | **Helga V. Toriello**[3] | **Dong Li**[4,5,6] | **Elizabeth J. Bhoj**[4,5,6] | **Hakon Hakonarson**[3,4,6] | **Beverly Nelson**[7,8] | **Sarah Gluschitz**[9] | **Ruth H. Walker**[10,11] | **Andrew K. Sobering**[1,12,13]

[1]Department of Biochemistry, St. George's University School of Medicine, St. George's, Grenada

[2]Augusta University/University of Georgia Medical Partnership Campus of the Medical College of Georgia, Athens, Georgia, USA

[3]Department of Pediatrics and Human Development, Michigan State University, East Lansing, Michigan, USA

[4]Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

[5]Division of Human Genetics, Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

[6]Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

[7]Pediatrics Ward, Grenada General Hospital, St. George's, Grenada

[8]Clinical Teaching Unit, St. George's University School of Medicine, St. George's, Grenada

[9]Department of Anatomical Sciences, St. George's University School of Medicine, St. George's, Grenada

[10]Department of Neurology, James J. Peters Veterans Affairs Medical Center, Bronx, New York, USA

[11]Department of Neurology, Mount Sinai School of Medicine, New York City, New York, USA

[12]Department of Basic Sciences, University of Georgia Health Sciences Campus, Augusta University/University of Georgia Medical Partnership, Athens, Georgia, USA

[13]Windward Islands Research and Education Foundation, St. George's, Grenada

Correspondence
Mary Maj and Andrew K. Sobering, Department of Biochemistry, St. George's University School of Medicine, St. George's, Grenada.
Email: mmaj@sgu.edu (M. M.) and andrew.sobering@uga.edu (A. K. S.)

Abstract

Background: *SYNJ1* encodes Synaptojanin-1, a dual-function polyphosphoinositide phosphatase that is expressed in the brain to regulate neuronal synaptic vesicle dynamics. Biallelic *SYNJ1* variants cause a spectrum of clinical manifestations, from early onset parkinsonism to developmental and epileptic encephalopathy.

Methods: Proband-only exome sequencing was used to identify a homozygous *SYNJ1* pathogenic variant in an individual with epileptic encephalopathy. Sanger sequencing was used to confirm the variant.

Results: We present an Afro-Caribbean female who developed uncontrollable seizures shortly after birth, accompanied by developmental delay and severe generalized dystonia. She had homozygosity for a novel c.242-2A>G variant

Mary Maj and Christie L. Taylor authors contributed equally.

in *SYNJ1* with both parents being heterozygous carriers. An older sister was reported to have had a similar presentation but was not examined. Both siblings died at an approximate age of 16 years.

Conclusions: We report a novel pathogenic variant in *SYNJ1* present in homozygosity leading to developmental and epileptic encephalopathy. Currently, there are only 4 reports describing 10 individuals with *SYNJ1*-related developmental and epileptic encephalopathy. This case expands the clinical knowledge and the allelic heterogeneity associated with *SYNJ1* variants.

KEYWORDS

developmental and epileptic encephalopathy, synaptojanin 1, *SYNJ1*

1 | INTRODUCTION

SYNJ1 (OMIM 604297) encodes synaptojanin-1 (SYNJ1; PARK20; EC: 3.1.3.36) a soluble lipid enzyme that is enriched in brain tissue and concentrated at synapses (Haffner et al., 1997; McPherson et al., 1996). The *SYNJ1* gene encodes a member of the inositol 5-phosphatase family of enzymes which contains an N-terminal Sac1 inositolphosphatase domain and a central 5′-inositolphosphatase domain (5′PP). The 5′PP domain catalyzes the dephosphorylation of phosphoinositides such as phosphatidylinositol-(3,4,5)-triphosphate [PIP3] at the D-5 position. The Sac1 domain catalyzes the dephosphorylation of other phospholipids such as phosphatidylinositol-3-P [PI3P] and phosphatidylinositol-4-P [PI4P] (Mani et al., 2007). Synaptojanin-1 is recruited to synaptic membranes by the association of its C-terminal proline-rich domain to binding partners that contain SH3-domains (McPherson et al., 1994). The balance of phosphoinositides, specifically, the concentration of phosphatidylinositol-(4,5)-bisphosphate [PIP2], is required for proper neurotransmission. Dephosphorylation of [PIP2] is crucial for uncoating of the clathrin lattice during synaptic vesicle turnover (Di Paolo & De Camilli, 2006), thus SYNJ1 is essential for synaptic vesicle recycling (Harris et al., 2000) and transmission of neuronal impulses across synapses.

Pathogenic variants in *SYNJ1* are implicated in human neurological disorders with a range of clinical severity and a general trend of genotype/phenotype correlation. Individuals who have either biallelic missense variants or at least one missense variant in combination with a predicted loss-of-function allele are often associated with PARK20 (OMIM 615530), a form of atypical early-onset parkinsonism (Hong et al., 2019; Kirola et al., 2016; Krebs et al., 2013; Kumar et al., 2020; Lesage et al., 2021; Quadri et al., 2013; Taghavi et al., 2018). This form of parkinsonism is rarely responsive to carbidopa/levodopa treatment (Ben Romdhan et al., 2018; Rauschendorf et al., 2017).

Biallelic truncating variants or biallelic predicted loss-of-function variants that reduce the activities of both the Sac1 and the 5′PP catalytic activities tend to be associated with a more severe developmental and epileptic encephalopathy (OMIM 617389). To our knowledge, there are currently four reports describing 10 individuals who have a biallelic predicted loss of *SYNJ1* function (Al Zaabi et al., 2018; Dyment et al., 2015; Hardies et al., 2016; Samanta & Arya, 2020). Here we present a 14-year-old female who had homozygosity for a novel pathogenic c.242-2A > G variant in *SYNJ1*. We describe the variant and associated clinical features of this individual to expand the genetic and phenotypic spectrum of this disorder.

2 | CLINICAL REPORT

2.1 | Case report

An Afro-Caribbean female presented at 14 years old at a pro bono medical genetics outreach clinic. The affected individual and her family reside on a small geographically-isolated island that lacks most medical services (Sobering et al., 2020). Most of her early records, including brain imaging, were lost in a natural disaster that destroyed the infrastructure of the island. The report of her past medical history was based on recollections of the mother and her consulting pediatrician.

The mother recalled that her affected daughter was floppy at birth and developed seizures on the first day of life. A detailed description of her seizures was not available. She had poor feeding as an infant and required bottle feeding throughout her life. From the age of about 6 to 13 years, she would consume approximately six 8-ounce bottles per day. At approximately 13 years, her feeding diminished steadily until her demise at age 16 when she was taking only one to two bottles per day.

On examination at age 14, she displayed severe muscle atrophy and cachexia. She had contractures of the limbs and generalized dystonia including dystonic neck extension and *risus sardonicus*. She also had severe spinal scoliosis. Global developmental delay was evident; she never developed any speech or language, did not smile, and did not form eye contact although there was a normal pupillary light response. Her facial features included apparent hypertelorism and asymmetrical positioning of the ears (Figure 1).

She was given carbamazepine which effectively controlled her seizures. A brain computed tomography scan was reported to have been obtained at 10 years of age, but neither the images nor the radiology report was available. An electroencephalograph was not performed. The family reported that there was an older sister with a similar presentation who died at approximately 16 years of age. The parents denied consanguinity. A compilation of the clinical features of the individual we present and the other known patients who have biallelic *SYNJ1* pathogenic variants can be found in the supplemental material (Table S1).

2.2 | Genomic analysis

Purified DNA was sent to a research lab for analysis. Proband-only exome sequencing revealed a homozygous pathogenic variant in *SYNJ1* c.242-2A > G (NM_003895.3). By the ACMG classification system, this variant is classified as pathogenic using the parameters: PVS1 + PS2 + PM2 (Richards et al., 2015). Homozygosity for the variant in the proband and carrier status of both parents was confirmed by Sanger sequencing.

3 | DISCUSSION

Biallelic variants in *SYNJ1* lead to a phenotypic spectrum of severity. When the phenotype is one of parkinsonism, it has been classified as PARK20 (OMIM 615530). This is typically of early onset but can also develop at a later age. Specifically, homozygosity of the recurrent p.(Arg258Gln) missense change is associated with a young age of onset (Krebs et al., 2013; Lesage et al., 2021; Olgiati et al., 2014; Quadri et al., 2013). Homozygosity for several other *SNYNJ1* missense variants such as p.(Arg459Pro), p.(Arg459His), p.(Arg839Cys), and p.(Tyr832Cys) can also cause the parkinsonism phenotype (Kirola et al., 2016; Kumar et al., 2020; Lesage et al., 2021; Taghavi et al., 2018), as can compound heterozygosity for various truncating and missense variants (Ben Romdhan et al., 2018; Hong et al., 2019; Lesage et al., 2021; Rauschendorf et al., 2017). Individuals with parkinsonism due to

FIGURE 1 A 14-year-old individual affected with *SYNJ1*-related developmental epileptic encephalopathy. Severe generalized dystonia, muscle atrophy, contractures, scoliosis, apparent hypertelorism, and *risus sardonicus* are evident

compound heterozygosity for missense variants in *SYNJ1* have not been described. There is one report of a typical Parkinson's disease presentation in two siblings who have homozygosity for the p.(Tyr832Cys) variant (Xie et al., 2019). This same variant was later also described by Lesage 2021 who noted slow parkinsonism progression.

In contrast, critical reduction, or loss of both the Sac1 and the 5′PP phosphatase functions cause a more severe phenotype characterized by developmental and epileptic encephalopathy (OMIM 617389). Individuals with this presentation typically have biallelic predicted loss-of-function *SYNJ1* variants that are either homozygous or compound heterozygous (Al Zaabi et al., 2018; Dyment et al., 2015; Hardies et al., 2016; Samanta & Arya, 2020). Decreased enzyme activity was demonstrated in functional studies of *SYNJ1* with homozygosity of the p.(Tyr888Cys) missense variant which was found in an individual who had this severe presentation (Hardies et al., 2016). The mechanisms underlying the specific phenotype–genotype correlations due to the severity of *SYNJ1* mutations, and implications for dysfunction of synaptic neurotransmission, correlate intriguingly with the increasing evidence for synaptic dysfunction in both Parkinson disease and dystonia (Ponterio et al., 2022; Scarduzio et al., 2022).

The *SYNJ1* c.242-2A > G variant we describe is predicted to cause the loss of the splice acceptor site for intron 2. Following this prediction, splicing of the mRNA formed with this mutation would generate an in-frame deletion of exon 3 with the substitution of cystine for serine at amino acid position 81. The predicted loss of exon 3 would lead to the deletion of 29 amino acids from the encoded protein, slightly upstream of the highly conserved Sac1 site. Future studies would need to be done to verify the functional consequences of the mutation on the mRNA, and the effect on the encoded protein. The variant we report, and the other known variants of *SYNJ1*, are shown in Figure 2.

Because of the observed spectrum of clinical severity based on genotype we propose to clarify the taxonomy of the *SYNJ1*-related disorders with a gene name and phenotype dyadic description (Biesecker et al., 2021). Following this proposed convention, the two main phenotypes of biallelic *SYNJ1* variants would be '*SYNJ1*-related parkinsonism' and '*SYNJ1*- related developmental and epileptic encephalopathy'. The individual we describe presented with clinical features similar to the other patients who have developmental and epileptic encephalopathy, thus it is likely that the variant we report leads to the loss of SYNJ1 phosphatase activity.

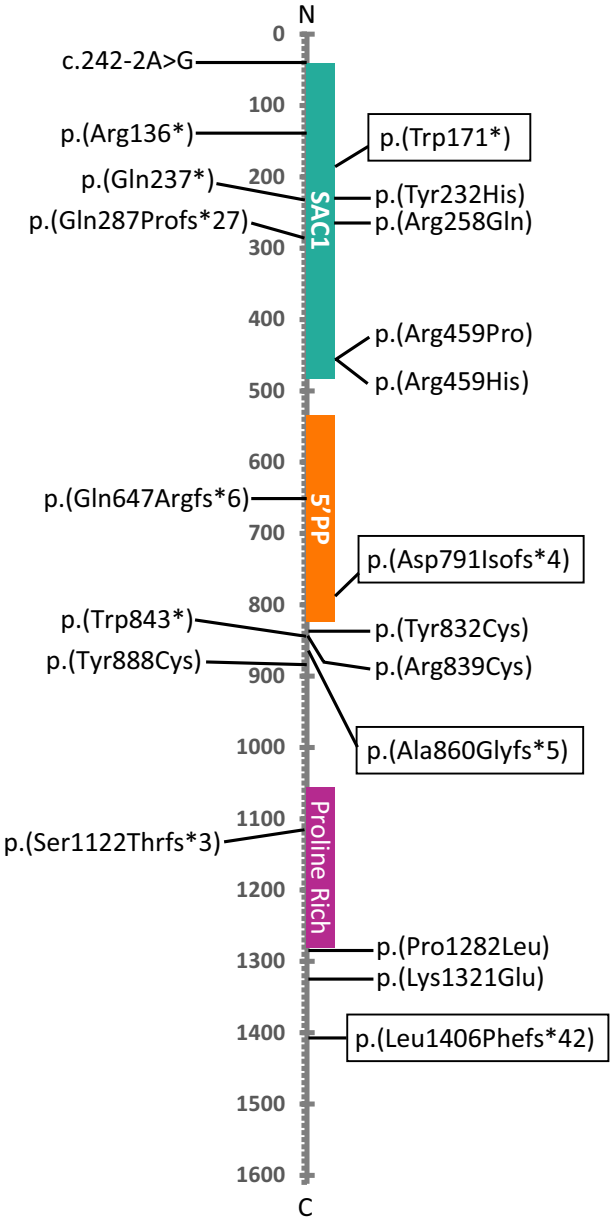

FIGURE 2 Protein domains of SYNJ1 and its known variants. Pathogenic variants associated with *SYNJ1*-related developmental and epileptic encephalopathy are on the left. Variants associated with *SYNJ1*-related parkinsonism are on the right. The predicted truncating variants annotated with boxes are found in individuals who have parkinsonism but with compound heterozygosity for a missense variant in *SYNJ1*. The Sac1 phosphatase domain is in green, the catalytic 5′PP domain is in orange, and the proline-rich domain is in purple

4 | MATERIALS AND METHODS

4.1 | Editorial policies and ethical considerations

Ethical oversight and approval of this study was provided by the St. George's University Institutional Review Board.

Verbal and written consent was obtained from both parents of the affected individual for genetic testing, release of clinical history, and publication of photos. Due to the small population size of the community where the patient and family reside, our IRB has requested that we do not reveal their precise nationality or geographic locations.

4.2 | DNA analysis

DNA was isolated from blood with the PureGene kit (Qiagen). Proband-only research exome sequencing was obtained to a mean coverage depth of 64×. Exome capture from the DNA of the affected individual was obtained with the Aglient V5 Exome Kit (Agilent), guided by the manufacturer's protocols. The libraries were subsequently sequenced for 101 cycles with a paired-end mode on the Illumina HiSeq 2500. Raw reads were aligned to the reference human genome using the Burrows-Wheeler Aligner (BWA) (Li & Durbin, 2009). Single-nucleotide variants and small insertions/deletions were captured using the genome analysis tool kit (GATK) (DePristo et al., 2011). ANNOVAR (Wang et al., 2010) and SnpEff (Cingolani et al., 2012) were used to functionally annotate the variants. Variants generated were filtered against public variant databases (dbSNP, 1000 Genomes Project, NHLBI ESP6500SI, gnomAD, and Kaviar) and an additional >5000 exome samples previously analyzed in our database hosted at Center for Applied Genomics (CAG) at The Children's Hospital of Philadelphia with a minor allele frequency of 1% (CAG database PMID accession numbers: 31263281 and 29,905,864). Subsequent gene prioritization was performed based on deleterious prediction and biological relevance by referring to the OMIM and HGMD. Sanger sequencing confirmed that the affected individual was homozygous for the *SYNJ1* variant and that both parents were heterozygous carriers.

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AUTHOR CONTRIBUTIONS

MM, KL, and AKS wrote the first draft of this manuscript. CLT, SG, and AKS compiled the supplemental table and created the figures. HVT, EJB, BN, and RHW provided care and clinical characterizations. Genomic analysis was provided by DL, EJB, and HH. AKS coordinated the project from its inception. All authors approved the final draft. The relatively large number of authors associated with this piece is due to the international collaborative aspect of the project.

ETHICS STATEMENT

This study was performed in accordance with the ethical standards detailed in the Declaration of Helsinki.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Mary Maj https://orcid.org/0000-0002-9258-2823
Dong Li https://orcid.org/0000-0002-2265-6727
Elizabeth J. Bhoj https://orcid.org/0000-0001-5748-3507
Hakon Hakonarson https://orcid.org/0000-0003-2814-7461
Andrew K. Sobering https://orcid.org/0000-0002-9251-2614

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SUPPORTING INFORMATION

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