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A *de novo* heterozygous missense *BSCL2* variant in 2 siblings with intractable developmental and epileptic encephalopathy

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ABSTRACT

Purpose: We present the case of 2 siblings with profound refractory epilepsy and neurological regression that began at the ages of 3 and 6 months. Diagnosis remained elusive despite extensive metabolic and genetic workups, including use of a targeted next-generation sequencing panel for epilepsy genes.
Methods: Whole-exome sequencing was performed for the 2 siblings and their unaffected parents, in addition to fibroblast cell culture, RNA extraction and reverse-transcription, and cDNA PCR. Brain tissue from one of the siblings was collected post-mortem for neuropathological examination, including histology and immunohistochemistry.
Results: A*de novo* nucleotide change (c.566 T > A; p.(Met189Lys)) in exon 4 of the *BSCL2* gene was detected in the 2 siblings, and confirmed by Sanger sequencing. This variant was absent in the parents and in a third, unaffected sibling.
Conclusion: Given the*de novo* nature of the variant, its absence from public and in-house databases, our *in silico* pathogenicity predictions, and co-segregation of the variant with the disease phenotype, we believe that this novel variant is associated with the epileptic encephalopathy phenotype of the 2 siblings. Our findings provide the first evidence of an association between a heterozygous *BSCL2* variant and developmental and early infantile epileptic encephalopathy. Further functional studies will be needed to elucidate the pathophysiological mechanisms underlying this new *BSCL2*-associated phenotype.

1. Introduction

The last 20 years have seen great advances in our understanding of the genetic basis of epilepsy. Next-generation sequencing (NGS) technologies have enabled the discovery of hundreds of genes associated with idiopathic epilepsies, in particular early infantile epileptic encephalopathies [1–4].

To date, pathogenic variants in the *BSCL2* gene have been associated with 4 distinct phenotypes: congenital generalized lipodystrophy type 2 and dominant upper and/or lower motor neuron diseases. Most of the variants implicated in congenital generalized lipodystrophy type 2 (Berardinelli-Seip syndrome type 2; MIM: #269700), a recessive inheritance disorder, are truncating variants predicted to cause severe disruption of the protein seipin [5]. Hereditary motor neuropathy type Va (MIM: #600794) and Silver syndrome (SPG17; MIM: #270685) are dominant inheritance disorders in which a role of the missense variant restricted to the N-glycosylation (N−X−S/T) motif of *BSCL2* has been proposed [6]. A 2013 report [7] described an autosomal recessive progressive encephalopathy with or without lipodystrophy (PELD or Celia's encephalopathy; MIM:#615924) in 3 Spanish families. All patients carried the same pathogenic variant (c.985C > T) on at least 1 allele, indicating a founder effect. This variant causes cryptic splicing,

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leading to skipping of exon 7 in *BSCL2*. The phenotype was severe and resulted in the deaths of 5 children between the ages of 6 and 8 years. Most but not all affected patients exhibited some signs of lipodystrophy, and the 5 children who ultimately died developed progressive encephalopathy with psychomotor regression, loss of speech, cognitive decline, spasticity, and seizures between the ages of 2 and 3 years [7]. The same homozygous nonsense *BSCL2* variant was later described in a patient with intractable epileptic encephalopathy, autistic behavior, repetitive and stereotypic hand movements, repetitive upward staring, ataxia, generalized hypertonia, and severe global developmental delay [8]. Recently, our group reported that the c.974dupG variant also leads to skipping of exon 7 of *BSCL2* and is responsible for a variant of Celia's encephalopathy with variable phenotypic expression [9].

Here, we report the case of 2 siblings who had severe intractable epilepsy and neurological regression without lipodystrophy or metabolic alterations and who both carried a *de novo* heterozygous missense *BSCL2* variant that we detected by whole-exome sequencing (WES) in a family quartet.

2. Methods

2.1. Patients

The first patient (index case) was a 10-year-old boy born to unrelated parents (first pregnancy). The mother had generalized epilepsy during adolescence but was not receiving any treatment during pregnancy. At 6 months of age the boy developed a febrile illness during which he presented multiple generalized tonic-clonic seizures and was admitted to an intensive care unit. An electroencephalogram (EEG) revealed slow cerebral activity (diffuse distributed delta-theta wave activity) and focal anomalies in the Rolandic and temporal regions of the right hemisphere. Biochemical analysis of cerebrospinal fluid (CSF) revealed leukocytosis with a predominance of mononuclear cells. Viral meningoencephalitis was suspected but PCR was negative for herpesvirus and other viruses. Brain MRI revealed no findings of note. The patient began treatment with valproic acid.

During the following months, the patient experienced febrile and afebrile generalized tonic-clonic seizures every 1–2 weeks, and levetiracetam was added to the valproic acid regimen. Psychomotor development was normal until 6 months of age (social smile at 3 months and sitting at 6). The patient acquired autonomous gait at 20 months of age but at 24 months exhibited evident delays in social skills. Subsequently, he experienced episodes of behavioral arrest with eyelid myoclonus of several seconds in duration compatible with absences. These absence episodes were sometimes associated with a loss of postural tone and sudden falls indicative of atonic seizures. An EEG at 2 years and 3 months of age showed slow basal activity and frequent paroxysms in the posterior quadrant of the right hemisphere. Increases in paroxysms and generalized spike-and-wave discharges at 2–3 Hz were observed during sleep. Ethosuximide was added to the valproic acid + levetiracetam regimen. Analyses of acid-base balance, liver and kidney profiles, basic metabolic screening (including ammonium, lactate, blood amino acids, and urine amino acids and organic acids), transferrin glycosylation, copper. and ceruloplasmin, and biotinidase activity revealed no findings of note. Biochemical analysis of CSF was normal: no abnormalities in CSF neurotransmitter profiles or in levels of lactate, amino acids, folate, or pyridoxine were observed. After 12 months without a seizure levetiracetam was removed from the patient's regimen.

At 4 years of age, generalized tonic seizures reappeared and phenobarbital was added to the treatment regimen. The patient continued treatment with valproic acid, ethosuximide, and phenobarbital, but seizure control was not achieved. The patient's epilepsy remained uncontrollable for the following years. Between the ages of 6 and 8 the patient followed a ketogenic diet, which failed to yield any improvements in seizure control.

The boy currently attends a special school and has moderate intellectual disability and autism spectrum disorder. He can form sentences of 2–3 words and understands simple commands. He has a mildly ataxic gait. His epilepsy is drug-resistant and he experiences 1–2 tonic or absence seizures per week. He is currently being treated with valproic acid, zonisamide, and clobazam. He does not have lipodystrophy.

The second patient, who was the younger sister of the index case, exhibited normal psychomotor development during the first months of life. At 3 months of age she presented episodes of asymmetric flexor spasms of the upper and lower extremities with right-side predominance and ocular deviation to the right. An initial EEG showed frequent independent multifocal epileptiform activity in both hemispheres during sleep and poorly structured baseline brain activity for the patient's age, with diffusely distributed delta waves and low-voltage beta rhythms. A physical examination revealed no findings of note. Lipodystrophy was absent. A complete blood count, electrolytes and acid-base analysis, and liver and kidney profiles were normal. Basic metabolic screening including ammonium, lactate, blood amino acids, and urine amino acids and organic acids revealed no findings of interest. The results of analyses of transferrin glycosylation, copper and ceruloplasmin levels, and biotinidase activity were also normal. No alterations were detected in CSF neurotransmitter profiles or in CSF levels of lactate, amino acids, folate, or pyridoxine. Brain MRI was normal. After beginning treatment with valproic acid the patient remained seizure-free for 5 months, but began to show signs of mild psychomotor delay affecting motor skills. At 8 months of age she developed asymmetric tonic seizures. Clobazam was added to the valproic acid regimen and provided seizure control for the first few weeks. EEG continued to show slow cerebral activity consisting of an association of theta-delta waves and diffusely distributed low-voltage beta waves. During wakefulness focal epileptiform activity was observed in the parietal and occipital regions of the left hemisphere.

At 9 months of age the patient experienced status epilepticus that required admission to the intensive care unit. EEG showed slow brain activity and multiple frontal epileptiform anomalies. Multiple antiepileptic drugs (carbamazepine, vigabatrin, phenobarbital) failed to control the refractory status epilepticus and the patient died at 10 months of age.

2.2. Neuropathological examination

CNS tissues were taken from the 10-month-old sister post-mortem and fixed in formalin for 21 days. The patient's brain weight was 760 g. The cerebral hemispheres showed a normal gyral pattern (absence of polymicrogyria and pachygyria). The ventricles were centered and nondilated, and the corpus callosum was present. The tissues were embedded in paraffin for routine neuropathological examination, including histology and immunohistochemistry.

2.3. Whole-exome sequencing

Whole-exome sequencing of both siblings and their unaffected parents was performed at the National Center of Genomic Analysis (CNAG) in Barcelona, Spain. Paired-end multiplex libraries were prepared using an Illumina TruSeq DNA Sample Prep Kit according to the manufacturer's instructions and were enriched using SureSelect Human All Exon V5. This kit targets ~50 Mb corresponding to ~21,500 genes. The libraries were loaded onto Illumina flow cells for cluster generation prior to production of 100-base read pairs using a HiSeq2000 instrument following the Illumina protocol. Base calling and quality control were performed using the Illumina RTA sequence analysis pipeline according to the manufacturer's instructions.

2.4. Data analysis

Sequence reads were mapped to Human genome build hg19

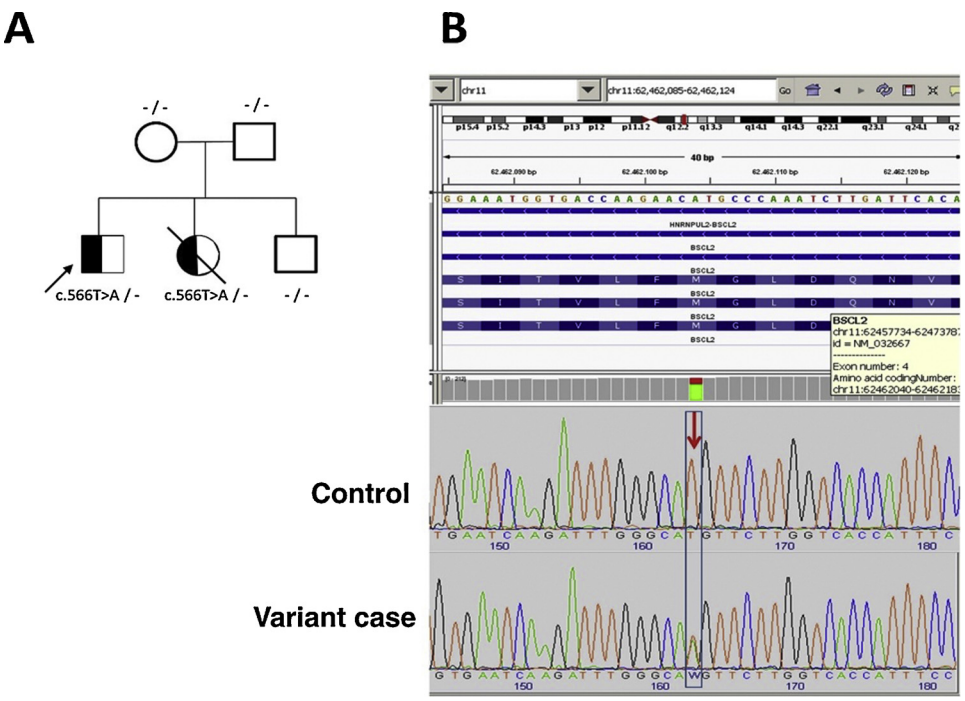

Fig. 1. Pedigree and electropherogram of the studied subjects. A) Pedigree of the subjects. Arrow, index case. B) Electropherogram of the c.566 T > A variant, red arrow (upper panel, control; lower panel, variant case). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

(GRCh37) using the GEM toolkit, allowing up to 4 mismatches, insertions/deletions within the read of up to 25 bp, and split-mapping for partially mapped reads. Reads were hard trimmed from the end of the read to the first base with a quality of over 10, and trimmed reads shorter than 40 bp were discarded. Unmapped reads were aligned using the BFAST aligner to enable detection of more distant matches. Alignment (.bam) files containing only properly paired, uniquely mapping reads without duplicates were processed using Picard Tools version 1.73 to add read groups and remove duplicates. Genome Analysis Tool Kit (GATK) version 1.6.5 was used for local realignment. Processed. bam files were subjected to variant calling for single nucleotide variants and small insertions and deletions using SAMtools version 0.1.19. Functional annotations were added using snpEff version 2.0.5d with the GRCh37.65 database. Human dbSNP version 137, population frequencies from the Exome Variant Server, and conservation and deleteriousness predictions from dbNSFP were annotated using snpSift version 1.3.4b. Variants identified in low-mappable regions of the genome or with a strong strand bias ($p \leq 0.001$) or coverage below 10 reads in at least one sample were removed from the list of candidate variants. The remaining variants were filtered using a bespoke R-based algorithm to detect potential disease-causing variants in an autosomal recessive and *de novo* dominant model. The variant detected was validated by Sanger sequencing of all members of the family, including the unaffected sibling.

2.5. Statistical analyses

Tolerance to missense *BSCL2* variants was quantified by determining the corresponding z-score. This score was calculated by initial regression of the total number of common (minor allele frequency > 0.5%) missense variants against the total number of common missense and synonymous variants observed for a given gene. The z-score is the corresponding studentized residual of the regression. Genes with a negative z-score have fewer missense variants than expected given the predicted mutation burden and are likely to be less tolerant of functional mutations.

The samples used to compare the *in silico* values (z-, GERP, and CONDEL scores) of the variant found in our patients with benign variants had been collected from 2504 individuals for the Phase 3 analysis of the 1000 Genomes Project (Fig. 2A).

2.6. RNA extraction and retrotranscription

Total RNA was extracted from fibroblasts from controls and the index case as per the manufacturer's instructions. The concentration and purity of each sample was determined by spectrophotometry (ND2000; Nanodrop). RNA samples were stored at −80 °C until use. RNA was reverse-transcribed using M-MLV reverse transcriptase (Invitrogen) as previously described [10].

2.7. cDNA PCR

BSCL2 cDNA was amplified with primers designed using Primer3Plus software (http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi). PCR conditions and primer sequences are available upon request.

3. Results

3.1. Genetic studies

For each individual, WES yielded about 7 GB of sequences that passed the Illumina filter. The mean percentage of bases with at least 10× coverage was 95.03% and the mean coverage for the 4 samples was 80 × . A mean of 16,266 novel variants (not identified in dbSNP) were identified in each family member. None of the results were compatible with homozygous or compound heterozygous scenarios. Only one protein-changing variant [c.566 T > A; p.(Met189Lys)] in exon 4 of the *BSCL2* gene (reference sequence NM_001122955.3) was found in the 2 affected siblings but not in either of the parents or the unaffected brother. This kind of heredity is compatible with germline mosaicism from one progenitor. The variant was not identified in 1006 ethnically matched controls or reported in the dbSNP (http://www.ncbi.nlm.nih.gov/SNP/), 1000 Genomes (http://www.1000genomes.org), Exome Variant Server (EVS; http://evs.gs.washington.edu/EVS), Genome Aggregation (gnomAD; https://gnomad.broadinstitute.org), or Exome Aggregation Consortium (ExAC; http://exac.broadinstitute.org) databases.

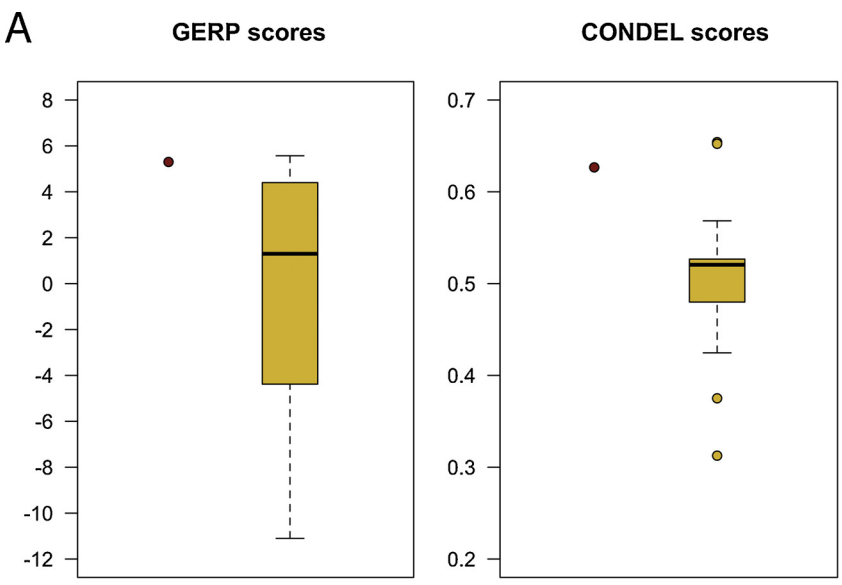

Fig. 2. A) Boxplot showing GERP/CONDEL scores (median and interquartile range) for missense variants described in the *BSCL2* gene. The score for the missense variant found in our patient is shown in red. Scores for the non-pathogenic missense variants in *BSCL2* are shown in yellow. For nonpathogenic variants, each boxplot represents the GERP/CONDEL scores of 2504 individuals from the Phase 3 analysis of the 1000 Genomes Project. B) Conservation across species of the polypeptide region of seipin surrounding the variant p.(Met189Lys) detected in our patients. Shading represents conserved amino acids. H. SAP, *Homo sapiens*; SUS S., *Sus scrofa*; RATTUS, *Rattus norvegicus*; MUS M., *Mus musculus*; XENOP., *Xenopus laevis*; DROSO., *Drosophila melanogaster*. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

We confirmed the presence of the variant by Sanger sequencing in both of the affected siblings and its absence in the parents and the unaffected sibling (Fig. 1). The mutation tolerance score for *BSCL2* was -0.4 (range -12.49, +16.00), indicating a low rate of benign missense variation. The affected amino acid was highly conserved, with a SIFT value of 0 (http://sift.jcvi.org/) and a GERP score of 5.3 (http://mendel.stanford.edu/SidowLab/downloads/gerp/index.html), which corresponds to one of the most evolutionary conserved positions within this gene (Fig. 2B). The predicted amino acid change (substitution of a hydrophobic for a positively charged amino acid) was considered highly likely to be pathogenic according to *in silico* predictions performed in Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/), Allamut (http://www.interactive-biosoftware.com/alamut-visual/), and CONDEL (http://bg.upf.edu/fannsdb/) software (Fig. 2B). The amino acid change is located in the intraluminal region of the seipin protein. Possible involvement of the c.566 T > A variant in splicing was evaluated using Human Splicing Finder (HSF, version 3.1, http://www.umd.be/HSF3). The program detected a potential splicing alteration with activation of exonic cryptic acceptor and donor sites (+72.47% and +15.32%, respectively) and the creation of a new exonic splicing silencer (ESS). To determine whether these *in silico* findings could actually result in compromised splicing, we performed cDNA PCR for *BSCL2* using different sets of primers spanning exons 2–7, but observed no differences between controls and the index case.

Using ACMG criteria, this variant can be classified as likely pathogenic: it is a *de novo* mutation absent from controls in public databases and it co-segregates in the family with the phenotype in question. Moreover, multiple lines of computational evidence support a deleterious effect of this variant on the gene. Finally, the negative z-score for this gene indicates a low rate of benign missense variation.

3.2. Neuropathology

Neuropathological studies revealed changes associated with acute neuronal hypoxia and a focal loss of neurons in the sections corresponding to the frontal, temporal, parietal, and occipital cortex. The cortex displayed normal lamination and no dysplastic or cytomegalic neurons were evident. Microglial activation and astrogliosis with the formation of microglial nodules were observed in the basal ganglia, in which neuronal cell density was preserved and nuclear inclusions were absent. No intranuclear ubiquitin-positive inclusions were observed in the brain. Microglial activation and astrogliosis were observed in the brainstem. The architecture of the cerebellum was preserved with normal Purkinje cell density and minimal neuronal cell loss from the dentate nucleus.

4. Discussion

The average exome contains just 0–5 *de novo* variants in coding regions [11,12]. Many novel epilepsy-associated genes have been detected through identification of *de novo* variants by WES trio analyses [1]. Together with *de novo* copy number variations, *de novo* point variants of large effect may account for most cases of intellectual disability [13] and autism spectrum disorder (ASD) [14,15]. These remarkable findings suggest that *de novo* variants may explain a considerable proportion of sporadic neurodevelopmental disorders.

The *BSCL2* gene encodes seipin, an integral membrane protein of the endoplasmic reticulum that is expressed at high levels in the brain [7,16]. While the function of seipin is not yet fully understood, it is highly expressed in most regions of the CNS, including the cerebral cortex, cerebellum, and hypothalamus [16,17]. Its broad tissue distribution suggests that it may be a multifunctional, tissue-dependent protein. Some studies have proposed a role in adipogenesis and lipid

metabolism [18–20], while others have provided evidence of potential neural involvement [21]. Seipin regulates excitatory synaptic transmission in cortical neurons [22,23] and is required for normal brain development and spermatogenesis [24], in addition to adipogenesis.

It has been speculated that seipin-truncating recessive variants associated with congenital generalized lipodystrophy type 2 cause loss of function, whereas dominant gain-of-function seipin variants (p.(N88S) and p.(S90 L) using the transcript reference sequence NM_032667.5) lead to dominant seipinopathies [25,26]. These 2 gain-of-toxic-function variants, described as c.455A > G, p.(Asn152Ser) and c.461C > T, p.(Ser154Leu), respectively (reference sequence NM_001122955.3), disrupt N-glycosylation and cause autosomal dominant motor neuron diseases [22] by impairing seipin's role in neurotransmission [23]. In 2013 [7], a homozygous *BSCL2* variant (c.985C > T, p.(Arg329Ter)) was described in 6 patients from the same geographic region in Spain who had an extremely severe neurodegenerative disorder involving seizures (Celia's encephalopathy or PELD). The same variant was subsequently described in homozygosity in an Iranian patient with developmental regression, epilepsy, and early death [8], and in compound heterozygosity in a female patient with regressive autism spectrum disorder, motor stereotypies, lower limb hypertonia, and, ultimately, frontal lobe syndrome [27]. This variant, c.985C > T, p.(Arg329Ter), produced a cryptic splicing site, causing skipping of exon 7 in *BSCL2,* giving rise the truncated seipin p.(Tyr289Leu*fs**64). This leads to much higher expression of *BSCL2*-201 transcript in the brain [7], which in homozygosity or compound heterozygosity is harmful to neurons [28]. In 2016, Opri et al. described 3 patients with progressive myoclonus epilepsy (PME) and recessively inherited congenital generalized lipodystrophy type 2 (CGL2) associated with known seipin variants [29]. The 2 variants implicated in the 3 cases were truncating. However, a recent study by our group found that one of the variants (c.974dupG) in fact results in skipping of exon 7 of *BSCL2* [9], as also occurs in PELD. Moreover, very recently Serino and coworkers (2019) reported that variant c.1076dupC (p.Glu360*) in homozygosity is associated with congenital generalized lipodystrophy, myoclonic seizures, and progressive neurological degeneration [30]. It therefore appears clear that seipin plays a crucial role in neuronal function, pointing to *BSCL2* as a candidate gene for epileptogenesis.

We have detected a novel heterozygous variant in *BSCL2* that 1) is a *de novo* variant; 2) is not present in any of the public databases or the 1372 chromosomes analyzed in the Iberian population; 3) co-segregates with the disease phenotype; and 4) affects a highly conserved amino acid of the seipin protein and is highly likely to be pathogenic according to the findings of several *in silico* prediction programs. Taken together, these findings strongly suggest that this novel *BSCL2* variant is highly likely to be involved in the phenotype of the 2 siblings described in this report.

5. Conclusions

This is the first report to link *BSCL2* to developmental and early infantile epileptic encephalopathy with a dominant pattern of inheritance. Moreover, our findings further extend the clinical spectrum of *BSCL2*-related disorders and add *BSCL2* to the epileptic encephalopathy-associated genes described to date. It should be noted that while the *de novo* nature of this variant and its co-segregation with the disease phenotype are highly suggestive of pathogenicity, these findings do not provide sufficient evidence of causality. Follow-up studies will be required to identify recurrence of this variant or provide functional proof of pathogenicity.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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