Correspondence

Regressive Autism Spectrum Disorder Expands the Phenotype of *BSCL2*/Seipin-Associated Neurodegeneration

To the Editor:

In 2013, Guillén-Navarro *et al.* (1) described 6 Spanish patients from Murcia, Spain, affected with a lethal neurodegenerative syndrome during infancy. All the patients were homozygous or compound heterozygous for a rare *BSCL2* exon 7–skipping variant. This disorder was called progressive encephalopathy with or without lipodystrophy, or Celia's encephalopathy (2). Since then, no other case has been published, and the phenotypic variability of this genetic event remains unknown. Here, we report a female patient with regressive autism spectrum disorder (ASD) who developed atypical parkinsonism in adulthood. The patient carried two different potentially pathogenic variants that affected splicing of exon 7 in *BSCL2*.

The patient was born in 1983 by spontaneous delivery. Her mother was born in Murcia. The patient's early development was unremarkable, and she was described as a playful toddler. She walked at 11 months of age and began to associate words at 18 months of age. However, slight behavioral disorders appeared by 3 years of age. At first, the behavioral issues consisted of anxiety and outbursts of temper, but later, more invasive rituals, progressive social withdrawal, attention problems, and sleep disorders emerged. In a few months, the patient exhibited a loss of communication and language skills. At 6 years of age, a clinical examination disclosed motor stereotypies (hand/arm flapping), trichotillomania, and lower limb hypertonia. She used an idiosyncratic language and could read a few words but was unable to write. Her ritualistic behaviors persisted. The patient was then diagnosed with regressive ASD. At 16 years of age, Bichat's fat pads, strabismus, bilateral worsening of dystonic hypertonia, and extrapyramidal and pyramidal features were noted. A camptocormia emerged at 21 years of age. L-DOPA (600 mg/day) had no clear benefit after a 6-month follow-up. At 23 years of age, falls, dysphagia, and a marked frontal lobe syndrome appeared. Trichotillomania and stereotypies persisted as well. At 24 years of age, a follow-up exam indicated major rigidity. Eventually, she died of a pulmonary infection at 28 years of age.

Blood/plasma ammonia, ferritin, hexosaminidases A and B, triglycerides, lactic/pyruvic acids, and urinary organic acids were normal. Creatine deficiency, Niemann-Pick disease type C, Gaucher disease, and Wilson's disease were excluded. The standard karyotype, *MECP2* sequencing, analysis for fragile X syndrome trinucleotide expansion, and Huntington's disease test were unremarkable. Pathogenic variants of the *PLA2G6* gene were excluded. Electroencephalography, abdominal ultrasounds, echocardiography, fundus, and electromyography were normal. The brain magnetic resonance imaging disclosed bilateral atrophy of the caudate nucleus. At 26 years of age, the patient underwent a dopamine transporter single-photon emission computed tomography (123I-FP-CIT DAT)* scan, which confirmed bilateral dopaminergic denervation of the caudate nucleus. Array comparative genomic hybridization (180K, Agilent Technologies, Santa Clara, CA) revealed a 1.3 Mbp 16p13.11 duplication inherited from the patient's mother (arr[GRCh38](14874998_16173449)x3mat) (Figure 1A). The causal role of this duplication was unclear because it is usually considered a susceptibility locus for ASD (3,4). However, the severity of the patient's autistic regression and neurodegenerative progression via dopaminergic denervation led to further investigations. Trio-based whole-exome sequencing was performed. Target enrichment was achieved with the SeqCap EZ MedExome kit (Roche, Madison, WI). Paired-end (2 × 150 bp) sequencing was completed using a NextSeq 500 High Output kit (Illumina, San Diego, CA). Rare variant prioritization was performed according to the different modes of inheritance in Online Mendelian Inheritance in Man (OMIM) disease-causing genes and databases for patients (HGMD, ClinVar) and control individuals (gnomAD). The most convincing variants were two [NM_001122955.3] (*BSCL2*) transitions, c.985C>T and c.1004A>C; each was inherited from one parent (Figure 1B). The c.985C>T transition variant has been previously reported in patients living in Murcia (1). This variant is predicted to create a stop codon, p.(Arg329*). However, the authors showed that this variant could also affect an exonic splicing enhancer, leading to exon 7 skipping, thus creating a frameshift, p.(Tyr289Leu64) (Figure 1D). Haplotype analysis suggested a founder effect. While the c.1004A>C variant is responsible for the p.(Gln335Pro) substitution, in silico predictions were also in favor of exon 7 skipping. Retrotranscription was performed on RNA extracted from Epstein-Barr virus–immortalized lymphoblastoid cells from both parents, with the RNeasy Mini Kit (Qiagen, Counterbluff, France), and polymerase chain reaction was performed on the complementary DNA product with the primers published by Sánchez-Iglesias *et al.* (5). Exon 7 skipping was observed for both parents. In addition, a second abnormal isoform was observed in the father, probably resulting from the use of an alternative splice site located 55 bp upstream to the physiological one, and also predicted to create a stop codon, p.(Ser317Argfs*65) (Figure 1C, E). Overall, the trio-based whole exome sequencing results were consistent with a diagnosis of *BSCL2*-related neurodegenerative syndrome.

BSCL2 (OMIM 606158) encodes seipin, an endoplasmic reticulum–resident protein linked to various genetic disorders (6–9). Loss-of-function variants were reported in congenital generalized lipodystrophy type 2 (OMIM 269700), a rare autosomal recessive disease (10,11). Two closely localized gain-of-function variants are linked to two distinct neurological phenotypes: distal hereditary motor neuropathy type V (OMIM 600794) and hereditary spastic paraplegia type 17 (SPG17, OMIM 270685) (12,13). Seipin may play a role in neurodevelopment and neurotransmission by regulating excitatory transmission and synaptic vesicle docking (6–8). In 2013, Guillén-Navarro *et al.* (1) reported on 6 children with autosomal recessive lipodystrophy associated with psychomotor regression and progressive dystonia. The children died at 7 to 8 years of age, mostly from pulmonary infection. In the autopsy samples, the abnormally skipped transcript was highly expressed in

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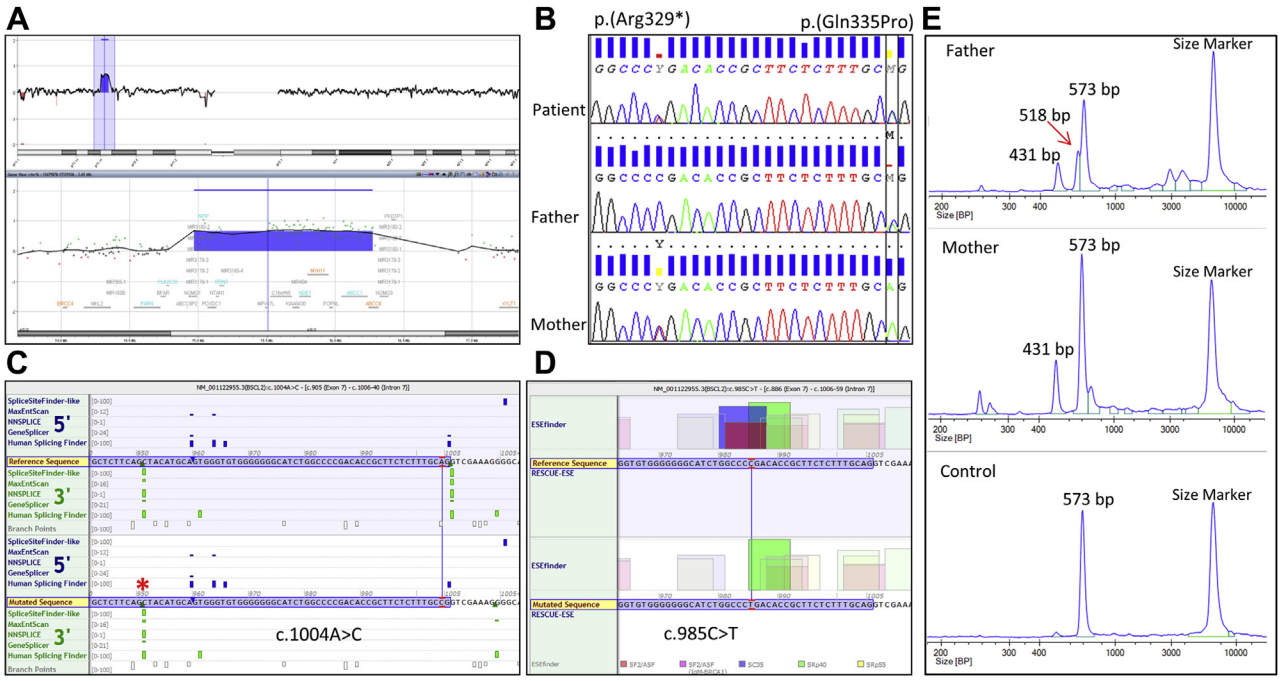

Figure 1. Cytogenetic and molecular investigations. **(A)** Array comparative genomic hybridization profile of the 16p13.11 duplication. **(B)** Sanger sequencing results of familial study. **(C)** In silico predictions of splicing effects of the c.1004A>C variant and alternative splice site (*) 55 bp upstream. **(D)** In silico prediction of exonic splicing enhancers for the c.985C>T variant. **(E)** Electropherogram profiles of the reverse transcriptase polymerase chain reaction products for *BSCL2* showing the exon 7 skipping for both parents (431-bp product) plus a second abnormal isoform for the paternal variant (518-bp product) probably consecutive to the use of an alternative splice site 55 bp upstream.

the central nervous system (1,2). Aggregated mutant seipin was found in ubiquitin-reactive neuronal nuclear inclusions in some of the patients (2). In the present study, the Bichat fat pads, behavioral disturbance before motor and cognitive decline, and neurological onset at 3 years of age are in accordance with previous descriptions (1). On the other hand, the clinical progression was surprisingly slow relative to previous reports. This may reflect disease variability as the results of the reverse transcriptase polymerase chain reaction analysis are not in favor of a less severe impact of the c.1004 variant on *BSCL2* function. However, this assay does not bring any quantitative estimation about the relative ration of the normal allele. Furthermore, severe regressive ASD followed by adult-onset parkinsonism with frontal lobe syndrome and dementia has never been described in seipin-associated neurodegeneration syndrome. Interestingly, a link between behavior and seipin haploinsufficiency was suggested in a murine model of anxiety (14). Basal ganglia dysfunction is often associated with behavioral, cognitive, and motor features. An autopsy study of an 8-year-old girl with seipin-associated neurodegeneration syndrome revealed major caudate atrophy (1). Our case confirms the involvement of basal ganglia, particularly in the caudate nucleus. In addition, CIT single photon emission computed tomography documented dopaminergic denervation for the first time in this syndrome. The 16p13.11 duplication may also be involved in the phenotype. However, the main features rather belong to the seipin-associated neurodegeneration spectrum. This suggest the need for genetic counseling when a predisposition factor in ASD is associated with a severe or an atypical phenotype. In that case we suggest that the possibility of a second site event should be assessed (15).

In conclusion, the present observation shows that *BSCL2* pathogenic variants can cause severe autistic regression in infancy and lethal atypical parkinsonism in adulthood.

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Article Information

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