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SPTBN1 HETEROZYGOUS MUTATION AND AUTISM SPECTRUM DISORDER: IS PATERNAL INHERITANCE POSSIBLE? A CASE REPORT FROM TÜRKİYE

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Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder defined by impairments in social communication and interaction, restricted and repetitive behaviors, and ritualized behavioral patterns. It was reported 70-90% hereditary transmission in ASD. Single gene variants on chromosomes 1, 2, 3, 5, 7, 15, 16 and 22 have been reported to be associated with ASD. SPTBN1 encodes a βII-spectrin, which plays a critical role in the organization of the neuronal cytoskeleton. Variants in the SPTBN1 gene can therefore lead to various neurological diseases. Until now, the SPTBN1 gene located at the 2p16.2 locus has been shown to be associated with both maternal inheritance and de novo mutations. However, to the best of our knowledge, paternal inheritance has not yet been reported. In this study, we present a female autism case with a paternally inherited heterozygous missense mutation in the SPTBN1 gene. Additionally, this case represents the first autism case carrying an SPTBN1 mutation reported from Türkiye.

Keywords: Paternal inheritance, Autism spectrum disorder, SPTBN1, Heterozygous mutation, Neurodevelopmental delay, Whole exome sequencing

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1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by challenges in social communication and interaction, as well as repetitive behaviors and restricted, ritualized patterns of behavior (Hirota and King, 2023). ASD, affecting around 2% of children with a male-to-female ratio of 4:1, is believed to have a strong genetic basis, with a hereditary transmission rate of 70-90% and associations with single-gene variants on chromosomes 1, 2, 3, 5, 7, 15, 16, and 22 (Genovese and Butler, 2023).

It has been reported that genetic testing in those diagnosed with ASD may be useful to provide information about screening for future diagnostic evaluations or to determine which type of intervention is more likely to respond (Wray et al., 2021). Through whole exome sequencing (WES), hundreds of chromosomal loci and genes susceptible to ASD have been identified in 6-37% of cases (Yin and Schaaf, 2017).

Variants in the spectrin genes SPTAN1, SPTBN1, SPTBN2, SPTBN4, and SPTBN5 have been associated with neurological disorders (Khan et al., 2022). The SPTBN1 gene (OMIM: 182790), has a cytogenetic localization of 2p16.2, is associated with various neurological disorders (Cousin et al., 2021).

A de novo nonsense variant and two de novo missense variants in the SPTBN1 gene have been detected in ASD probands from the Simons Simplex Collection (Iossifov et al., 2014). Additionally, rare inherited missense variants in SPTBN1 were identified in two Chinese ASD probands by Li et al. (2017). Rosenfeld et al. (2021) described seven unrelated individuals with heterozygous SPTBN1 variants, all of whom exhibited developmental delay and/or intellectual disability; three of these individuals were diagnosed with autism spectrum disorder, while a fourth showed autistic traits.

Zhou et al. (2022) reported the identification of further de novo loss-of-function and missense variants in SPTBN1 in ASD probands from both the MSSNG and SPARK cohorts. Furthermore, a two-stage analysis of 42,607 ASD cases, including 35,130 newly reported cases from the SPARK cohort, revealed SPTBN1 as a gene of exome-wide significance ($P<2.5E-06$). The association between SPTBN1 and ASD risk in this study was primarily driven by rare inherited loss-of-function variants passed from unaffected parents to affected children.

This study reports a female patient with autism spectrum disorder (ASD) who carries a paternally inherited heterozygous missense mutation in the SPTBN1 gene. To the best of our knowledge, this is the first documented case of paternal inheritance of an SPTBN1 mutation in an ASD patient, as previous reports have predominantly

focused on maternal inheritance and de novo mutations. Additionally, this case represents the first instance of an SPTBN1 mutation in an ASD patient in Türkiye. Considering the gender differences in ASD prevalence, the fact that this case involves a female patient further enhances its contribution to the field.

2. Case Presentation

A 4-year-6-month-old girl was admitted to child and adolescent outpatient clinic with speech delay, difficulty in transitioning to solid foods, self-injurious behaviors. She was exhibiting limited social interaction, displaying little interest in peers or play with toys. She was not using her index finger. Frustration and agitation ensue when her needs were not met, was leading to episodes of harmful behavior to herself and her mother. She had difficulty eating solid foods and therefore she usually fed by formula. She was diagnosed with epilepsy and was using sodium valproate 200 mg/day for epilepsy and risperidone 1 mg/day for behavioral problems.

In physical examination, tapered finger, pes planus, suspiciously short 4th and 5th metatarsals are inspected (Figure 1).

The patient had significant social and communicative impairments in mental status examination. Absences of eye contact, social smiles or joint attention, stereotypical behaviors (jumping), idiosyncratic behaviors such as laughter and vocalizations were notable features. She did not talk during examination.

Her mom gave a normal pregnancy and birth history. Hypotonia or hypertonia was not described. Because she did not hold breast and not sucked, she was not fed with breast milk.

She started walking when she was 19 months old. She does not speak and has not received toilet training.

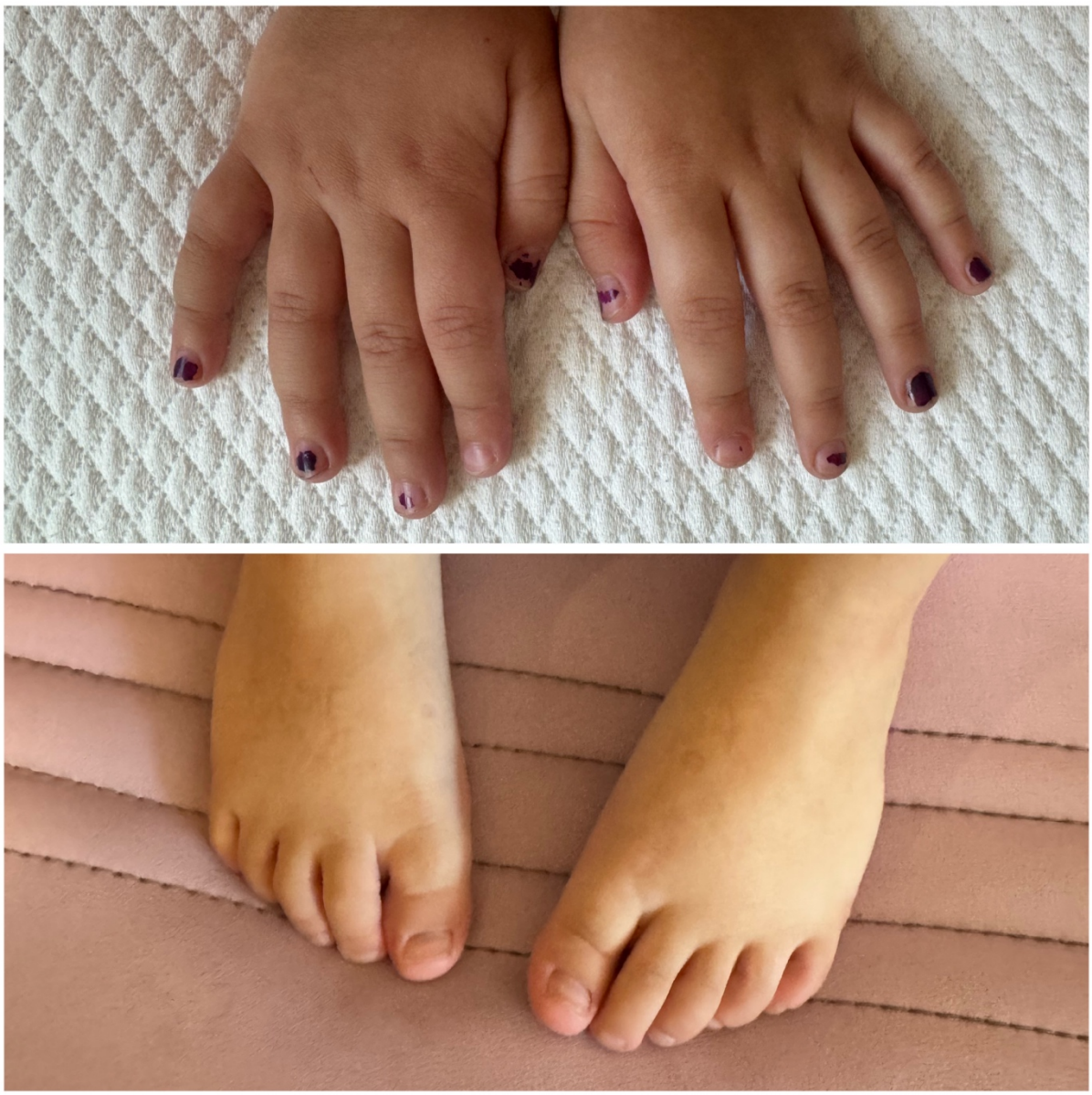

Figure 1. The patient's hands and feet.

Her general development was consistent with 12 months, language cognitive skills with 8 months, fine motor skills with 8 months, gross motor skills with 15 months and social skills and self-care skills with 12 months in her psychometric evaluation with Ankara Developmental Test Inventory.

The Childhood Autism Rating Scale was evaluated as 52 points.

Her EEG showed spike wave discharges originating from the left frontotemporal region 7-8 times. The magnetic resonance imaging (MRI) was within normal limits.

In WES analysis the presence of a (heterozygous) missense mutation in the SPTBN1 gene c.2044G>T (p.A682S) (NM_003128.2) (rs767613378) was determined. Sanger DNA sequence analysis was performed for "SPTBN1 gene c.2044G>T (p.A682S)" from the maternal and paternal DNA samples (no example was taken from his brother). While the mutation for the mother was determined to be normal, the father was considered heterozygous for the change mentioned. No microdeletion or microduplication was detected in the microarray analysis performed on the patient's DNA sample.

The patient's mother has diagnosed attention deficit hyperactivity disorder (ADHD) and bipolar disorder, and her father had mood disorder. Her brother had diagnosed of ASD and ADHD.

3. Results and Discussion

SPTBN1 encodes a βII-spectrin, which plays a critical role in the organization of the neuronal cytoskeleton. Variants in the SPTBN1 gene can therefore lead to various neurological diseases. Cousin et al. (2021), reported heterozygous mutations in the SPTBN1 gene were identified in 29 patients and six of them were exhibiting autistic features or had a diagnosis of ASD. In one patient, the mutation was inherited from the unaffected mother, while the others were reported to be de novo mutations.

In another study, seven cases with SPTBN1 mutation were identified and four of these cases were reported to have autistic symptoms. Among these cases, four had de novo mutation and one had maternal inheritance (Rosenfeld et al., 2021). Behavioral, neuromuscular, craniofacial and musculoskeletal changes have been described in the presented case series.

In a recent study involving whole-genome sequencing (WGS) of a cohort of 68 individuals from 22 families with ASD, potential pathogenic variants were identified in several known ASD genes, including SPTBN1. The study found that the identified variants in SPTBN1 were consistent with de novo mutations, meaning they occurred spontaneously in affected individuals and were not inherited from the parents (Tuncay et al., 2022).

Mutations in the SPTBN1 gene have been associated with a variety of neurological and developmental disorders, and their effects on the musculoskeletal system are also under investigation. SPTBN1 plays a crucial role in bone metabolism, specifically by regulating osteoblast proliferation, differentiation, and apoptosis (Jung and Wu, 2024). Although the direct link between pes planus (flatfoot) and SPTBN1 mutations has not been definitively established, this connection may be inferred due to the gene's role in the regulation of cytoskeletal and connective tissue proteins. Such a finding suggests a potential relationship that warrants further exploration. Other musculoskeletal anomalies, such as tapered finger and suspiciously short 4th and 5th metatarsals, may also be observed in individuals with SPTBN1 mutations (Rosenfeld et al., 2021). These conditions could point to a broader involvement of SPTBN1 in the development of structural abnormalities in the limbs. Clarifying these associations will require extensive genetic and phenotypic studies in the future.

Children diagnosed with ASD at the age of 4-5 may continue to have strict attitudes towards food variety and textures, and may still prefer smooth or textured foods (Al-Beltagi, 2024). In the case we presented, it was thought that feeding formula instead of solid food was related to the ASD diagnosis.

A 2019 meta-analysis and multidisciplinary consensus statement reported that exome sequencing is a first-line clinical diagnostic test for individuals with neurodevelopmental disorders (Srivastava et al., 2019). Genetic assessments can provide prognostic information by identifying an underlying genetic etiology. They can clarify the risk of recurrence of the condition and inform clinical management. They can also direct patients and families to condition-specific resources and supports (Savatt and Myers, 2021). In addition, genetic testing can provide patients and their caregivers with the ability to identify, treat, and/or prevent medical comorbidities at the time of diagnosis and conditions that may develop later in life (Sun et al., 2015). It can also help families understand the risk of recurrence in subsequent children and generations, allowing families and healthcare providers to identify neurodevelopmental disorders and initiate behavioral treatments at earlier ages (Narcisa et al., 2013)

Although maternal inheritance of SPTBN1 mutations has been previously reported, we present the first documented case in the literature of a female with ASD who carries a paternally inherited SPTBN1 mutation, representing the first such case reported from Türkiye. The clinical features observed in this patient were consistent with those reported in most previous studies; this revealed that there was no difference between maternal and paternal inheritance of the SPTBN1 gene. This study underscores the necessity for more in-depth studies on genetic variations within specific geographical and ethnic contexts, as further research is crucial to clarify the relationship between SPTBN1 and ASD.

Author Contributions

The percentages of the authors' contributions are presented below. All authors reviewed and approved the final version of the manuscript.

	D.A.A.	S.T.H.	M.F.C.
C	40	30	30
D	50	50	
S	100		
DCP	50	30	20
DAI	20	50	30
L	80	10	10
W	70	20	10
CR	60	30	10
SR	50	30	20
PM	50	40	10

C= concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision, PM= project management.

Conflict of Interest

The authors declared that there is no conflict of interest.

Ethical Consideration

Written informed consent was obtained from the patient for the case presentation, and necessary information was given to the patient. The research was conducted in accordance with the Principles of the Declaration of Helsinki.

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