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Distinct Autism Spectrum Disorder Phenotype and Hand-Flapping Stereotypes: Two Siblings with Novel Homozygous Mutation in *TRAPPC9* Gene and Literature Review

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Autism spectrum disorder · Intellectual disability · MRT13
TRAPPC9

Abstract
Objective: Pathogenic mutations of the *TRAPPC9* gene are the rare genetic causes of autosomal recessive intellectual disability (ID). There are several features that are not fully penetrant such as microcephaly, dysmorphic facial features, obesity, autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD), and brain abnormalities in *TRAPPC9* mutations. ***Methods:*** We performed whole-exome sequencing to evaluate 2 Turkish siblings with ASD and ID born to healthy and consanguineous parents. Parental samples were also analyzed, specifically targeting variants detected in these patients. ***Results:*** We present a novel homozygous mutation in the *TRAPPC9* gene, c.484G>T (p.Glu162Ter). Additionally, we aim to provide a more comprehensive understanding of the clinical features of a novel homozygous *TRAPPC9* mutation. In addition to ID, the siblings in this report suffered from ASD and specific stereotypes as hand-flapping behavior. ***Conclusion:*** Although there are inconsistencies in the presentation of ASD in *TRAPPC9* mutations, repetitive behaviors (hand-flapping) were typical in our cases and several previous reports. The current mutation was described to cause a homozygous premature termination codon that resulted in the absence of the *TRAPPC9* protein. We suggest that *TRAPPC9* mutations are not only related to ID but also to ASD and hand-flapping behaviors.

Introduction

Autism spectrum disorder (ASD), a highly heterogeneous neurodevelopmental disorder, is characterized by significant limitations in verbal and non-verbal social interaction, repetitive and restricted behavior and interest patterns, and a series of sensory presentations [American Psychiatric Association, 2013]. Intellectual disability (ID) involves problems in intellectual functions (problem solving, reasoning, learning) and adaptive behavior (social, conceptual, and practical skills) that appear before the age of 18 [Tassé et al., 2013]. These 2 conditions often coexist. Also, some ID candidate genes have frequently been determined in ASD. Since the advance of the exome or genome sequencing platforms, the detection of rare

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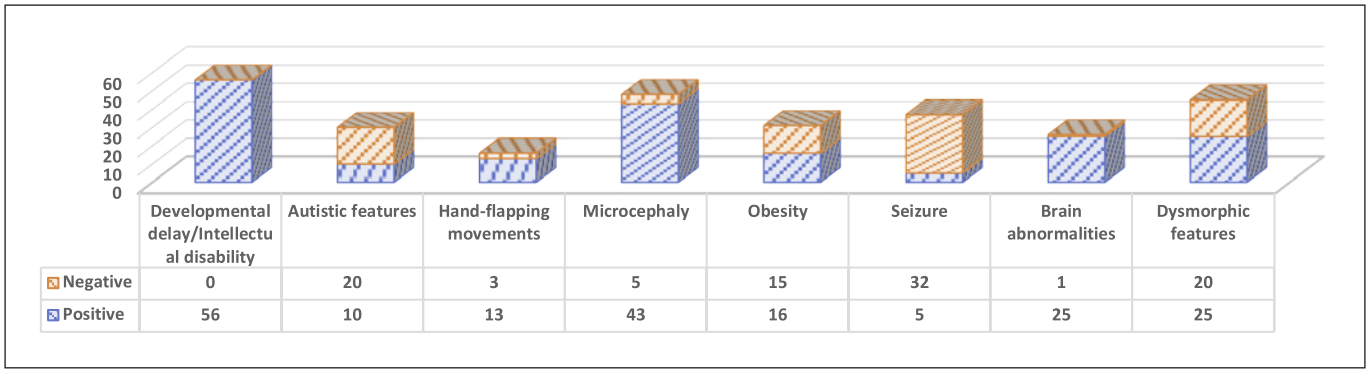

Fig. 1. Distribution of clinical features of patients with *TRAPPC9* mutations.

Table 1. Clinical features of patients with *TRAPPC9* mutations in the present study and previous reports

Clinical feature	Previous reports	This study (case 1)	This study (case 2)
Male/female	26/28	Female	Female
Developmental delay/intellectual disability	54/54	+	+
Autistic features	8/28	+	+
Hand-flapping movements	11/14	+	+
Microcephaly	41/46	+	+
Obesity	14/29	+	+
Seizure	5/35	–	–
Brain abnormalities	23/24	+	+
Dysmorphic features	23/43	+	+

genetic variants responsible for ID or ASD has improved significantly.

One of these rare genetic variants are pathogenic variants of *TRAPPC9* that are associated with autosomal recessive ID (MRT13, OMIM#613192). *TRAPPC9* involves 23 exons and encodes the NIK-and-IKK2-binding protein (NIBP). NIBP plays a role in the neuronal NF-κB signaling pathway that was associated with neuronal differentiation, axon growth, and myelination [Marangi et al., 2013]. In addition, the absence of *TRAPPC9* was associated with apoptotic signals in neurons causing an increased cell loss and development of microcephaly [Abbasi et al., 2017].

In the literature, pathogenic *TRAPPC9* mutations are associated with ID and developmental delay in all 54 reported cases [Mir et al., 2009; Mochida et al., 2009; Philippe et al., 2009; Koifman et al., 2010; Abou Jamra et al., 2011; Kakar et al., 2012; Marangi et al., 2013; Giorgio et al., 2016; Abbasi et al., 2017]. However, there are inconsistencies in other clinical findings of *TRAPPC9* mutations. In addition to ID and developmental delay, these features have been reported: microcephaly, dysmorphic facial features, obesity, ASD, stereotypical behaviors (hand-flapping behavior), attention-deficit hyperactivity disorder (ADHD), and brain abnormalities.

Herein, we present a novel mutation in the *TRAPPC9* gene, c.484G>T (p.Glu162Ter), in 2 Turkish siblings with ASD and ID born to healthy and consanguineous parents through whole-exome sequencing. Additionally, we aim to provide a more comprehensive understanding of the clinical features associated with a novel homozygous TRAPPC9 variant.

Methods

In our previous study, we evaluated patients who presented at the outpatient clinic of the Child and Adolescent Psychiatry Clinic and were diagnosed with ASD [Bolat and Bolat, 2021]. We included cases with no numerical or structural chromosome abnormalities detected using classical karyotype analysis, negative (wild type) genetic results for *MECP2* mutations in female cases, and normal CGG repeat sizes for *FMR1* testing in the male cases. After this process, the cases that were not pathogenic or likely pathogenic CNV carriers and whose parents were consanguineous were evaluated by whole-exome analysis. In our study, there were 3 fam-

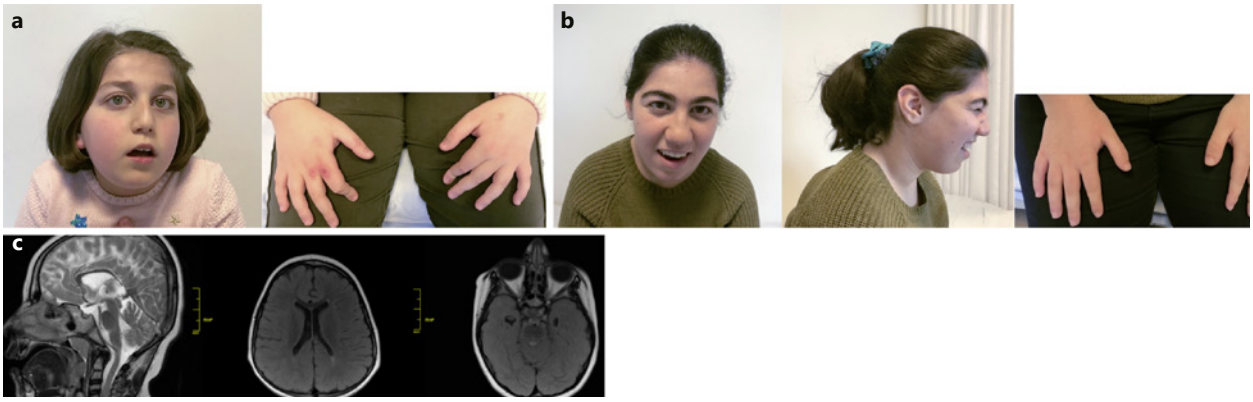

Fig. 2. Dysmorphic features of the 2 affected siblings. **a**, **b** Brachycephaly, a round face, full cheeks, prominent nasal bridge, short philtrum, a thin upper lip, small hands. **c** Brain magnetic resonance imaging (performed at 5 years of age) showed corpus callosum dsygenesis (T1-weighted sagittal section, asterisk) and areas of delay in myelination at the level of bilateral trigones, prominence in the temporal horns of bilateral lateral ventricles.

ilies matching these criteria, and whole-exome analysis was applied to them. Written consent was obtained from the legal guardians for each test applied in the diagnostic process. Approval from the local institutional review board and informed consent from the patients' parents was obtained prior to the genetic studies. Informed consent was obtained for clinical as well as genetic diagnostics and for publication of the data. A clinical geneticist, child psychiatrist, and child neurologist supervised the clinical examination. Clinical features of patients with *TRAPPC9* mutations in the present and previous reports are described in Table 1. Also, distribution of these features of patients with *TRAPPC9* mutations are shown in Figure 1. Dysmorphic features and brain magnetic resonance imaging findings are shown in Figure 2. The family pedigree is shown in Figure 3.

Genetic Testing

Genomic DNA (gDNA) was isolated from peripheral blood samples of the patients according to the QIAamp Blood kit protocol (Qiagen, Hilden, Germany). Exome enrichment was performed using Twist Comprehensive Human Exome according to manufacturer's instructions. Prepared library was sequenced on MGISEQ-2000 at 80-100X on-target depth with 150 bp paired-end sequencing. Bioinformatics analyses were performed using in-house developed workflow derived from GATK best practices at Intergen Genetic Diagnostic Center Ankara/Turkey. Raw reads were cleaned from adapter contamination during demultiplexing stage, therefore no further adapter cleaning was performed on FASTQ files. Alignment to GRCh38 was done using BWA-MEM 0.7.17 [Li and Durbin, 2010]. Subsequent sorting, duplicate marking, and base score recalibration steps were performed using GATK [van der Auwera et al., 2013]. Variant calling was performed using GATK HaplotypeCaller, and low quality variants were eliminated based on strand bias, read depth, and call quality parameters and other related parameters [van der Auwera et al., 2013]. Copy number variations were inferred using GATK GermlineCNVCaller [van der Auwera et al., 2013].

Variant Analysis and Classification

High quality variants were subjected to functional annotation using Variant Effect Predictor from ENSEMBL [McLaren et al., 2016]. Rare variants (MAF <1%) with high impact, unknown significance, and/or potential splice effects were prioritized. Other variants with potential effects on the observed phenotype were also analyzed. Variants of interest were visually checked on IGV [Robinson et al., 2011] and compared against an in-house disease variant database by Intergen Genetic Diagnostic Center Ankara/Turkey. Potential candidates were confirmed using targeted sequencing on Illumina MiSeq platform. Confirmed candidate variants were also tested with the same methods amongst the members of the family.

Results

We performed whole-exome analysis and identified clinically relevant pathogenic variants in 1 out of 3 families. There were 2 affected individuals in the same family. Our case 1 is a 16-year-old female. She is the first child born to a consanguineous, healthy Turkish couple. The mother did not have any complications in the pregnancy, and the patient was delivered at the 40th gestational week. It was stated that she was exposed to hypoxia during delivery. Birth weight was recorded as 3,000 g, but height and head circumference measurements were not recorded. There were no problems with breast milk intake, feeding, and swallowing after birth. At 3 months, the family noticed that the child was hypotonic. At 9 months, she was able to sit without support. She had delayed psychomotor development, which included walking at the age of

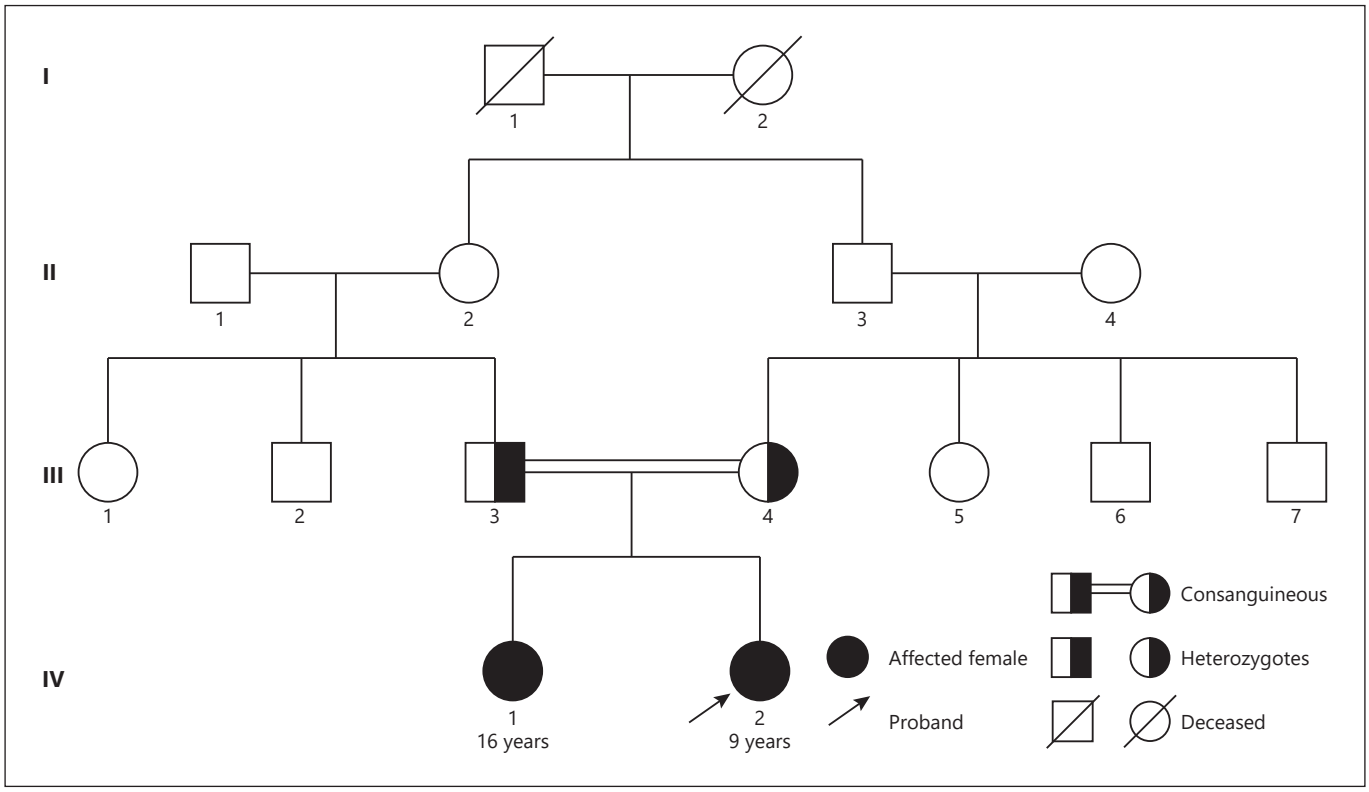

Fig. 3. Pedigree of the consanguineous family with the 2 patients.

4. Her language development is also delayed. First meaningful word use was at 4 years of age. She was first evaluated for developmental delay at the age of 1 year. This delay was initially thought to be due to hypoxic ischemic encephalopathy. Then, stereotypes such as flapping hands, rocking in the seat, and overreaction to sounds have started. After her stereotypes had begun, she was evaluated for Rett Syndrome. At that time, no mutation at the *MECP2* gene was detected. Another complaint at this period was sleep disturbance. She has been overweight since she was a baby. She used to be a hyperactive child and had jaw dislocations from the temporomandibular joint several times. Her current symptoms were the limitation of eye contact and communication skills, restricted interests, stereotypical movements, and learning difficulties. Self-care skills were not acquired. At the age of 16, she could speak only 5–6 words, but not sentences. There was no abnormal finding in her neurological examination. No history of trauma, seizure, or frequent infection was defined. At the age of 16 years, her height was 155 cm (−1.31 SD), her weight was 64 kg (0.93 SD), and her OFC was 52.2 cm (−2.88 SD). The current body mass index (BMI) of the case was 26.6. We do not have a previous BMI of the patient, whose family has always been reported to be overweight.

Our case 2 is a 9-year-old girl (the younger sister of the first patient) presented to the Child and Adolescent Psychiatry Outpatient Clinic with a previous diagnosis of ASD and ID based on the diagnostic criteria in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association [American Psychiatric Association, 1994]. The patient was delivered by cesarean section at the 40th gestational week because of the medical conditions of the older sister. The mother did not have any complications in pregnancy and delivery. After birth, the patient had feeding difficulties. No history of aspiration or pneumonia are described. At 7 months, she was able to sit without support. She had delayed psychomotor development, which included walking at the age of 2. Her language development is also delayed. She had hyperactivity and impulsivity. No history of trauma, seizure, or frequent infection was defined. She frequently makes short, scream-like sounds. There is strabismus (exotropia) in her right eye. Her neurological evaluation was normal. Neuroimaging findings are shown in Figure 2. At the age of 9 years, her height was 133 cm

(−1.92 SD), her weight was 40 kg (0.16 SD), and her OFC was 46.8 cm (−4.46 SD).

This case presented ASD symptoms in addition to developmental delay history. We evaluated the patient for ASD-related symptoms using the Childhood Autism Rating Scale (CARS). CARS is widely used in the diagnosis of autism and to distinguish children with autism from children with other developmental disorders. It is based on observation of the child and interview with the family. The instrument was developed by Schopler et al. [1980], and its validity and reliability in Turkish people has been demonstrated [Sucuoglu et al., 1996]. The interviewer determines the severity of ASD symptoms by evaluating 15 areas (relationships with people, imitation, emotional response, body use, object use, adaptation to change, visual response, auditory response, near-receptor response, anxiety, verbal communication, nonverbal communication, activity level, intellectual inconsistency, and general impression). A score of 30 or higher indicates the presence of ASD; our patient had a total score of 45. DSM-5 describes the diagnosis of autism spectrum disorder as based on "deficits in social skills" and "restrictive, repetitive patterns of behavior, interests or activities" [American Psychiatric Association, 2013]. Deficits in these areas belonging to this case are described below.

Speech, Language, and Social Difficulties

The parents of the patient described delayed motor and language development, reporting that she spoke her first word when she was 3 years old. Her language skills are still impaired. At the age of 9, she can make sentences containing a maximum of 2–3 words.

Restricted, Repetitive Behavior Patterns or Activities

Repetitive behavior patterns have been identified since 1 year of age. Since childhood, she had stereotypes of hand-flapping and rubbing hands with joining in the midline. In addition, she has restricted areas of interest. Excessive smelling or touching of objects and hypersensitivity to sounds cause impairment in daily functioning.

The initial diagnostic examinations included a complete metabolic workup, conventional karyotyping, chromosomal microarray test and MECP2 testing, which were all negative. We identified a homozygous nonsense mutation in chromosome 8 within the *TRAPPC9* gene c.484G>T (NM_031466.7) in the 2 siblings. This homozygous pathogenic variant resulted in a premature stop codon (p.Glu162Ter) and is not present in the gnomAD database (https://gnomad.broadinstitute.org/gene/ENSG00000167632). This variant is considered pathogenic based on criteria from Richards et al. [2015]. Parental samples were also analyzed specifically targeting those variants seen in the patients, and the father and mother were heterozygous for the same variant.

Discussion

In this report, we present a new nonsense mutation c.484G>T (p.Glu162Ter) in the *TRAPPC9* gene in 2 siblings with ID and ASD. The father and mother were heterogeneous for the same variant.

To date, 54 reported cases with mutations in *TRAPPC9* have been associated with ID and developmental delay [Mir et al., 2009; Mochida et al., 2009; Philippe et al., 2009; Koifman et al., 2010; Abou Jamra et al., 2011; Kakar et al., 2012; Marangi et al., 2013; Giorgio et al., 2016; Abbasi et al., 2017]. In line with the literature of cases with *TRAPPC9* mutations, both cases in our report had ID and developmental delay.

In addition to ID and developmental delay, *TRAPPC9* mutations have been associated with variable degrees of microcephaly, dysmorphic facial features, obesity, ASD, stereotypical behaviors (hand-flapping behavior), ADHD, and brain abnormalities. We determined all of these features in our cases. Both of our patients shared the same homozygous mutations in *TRAPPC9* with similar clinical presentations. Pathogenic variants that cause decrease or absence of *TRAPPC9* protein and transcripts with premature stop codons activate nonsense-mediated decay and result in various clinical presentations. To date, a genotype-phenotype correlation in *TRAPPC9* mutations has not been described for these clinical features.

Autistic features are a relatively rare phenotypic characteristic in patients with *TRAPPC9* mutations. Several cases with *TRAPPC9* mutations have been associated with both ID and ASD [Mortreux et al., 2018; Krämer et al., 2021]. A diagnosis of autism was reported in approximately 28.6% of the previously reported cases. Our case had severe deficits in verbal communication skills and repetitive/restrictive behaviors. Verbal communication deficits and ID were core phenotypes related to *TRAPPC9* deficiency, ASD symptoms and repetitive behaviors may vary. Wilton et al. [2020] reported a 27-year-old case with *TRAPPC9* mutation with an initial diagnosis of ASD, and they reported no progress in language development despite 15 years of speech therapy. There were some cases presenting autistic features like hand-flapping movements, but not classified as ASD. Although there are differences in the presentation of ASD and repetitive behaviors in *TRAPPC9* mutations,

repetitive behaviors (hand-flapping behavior) were typical in the previous reports of *TRAPPC9* deficiency cases that were presenting stereotypic behaviors. Hand-flapping movements were reported in approximately 78.6% of previously reported cases. Therefore, it strengthens the view that the typical repetitive movements in these cases are due to a *TRAPPC9* mutation.

Brain abnormalities, especially thinner corpus callosum, were also common that have supported the role of *TRAPPC9* mutations [Najmabadi et al., 2007; Mir et al., 2009; Mochida et al., 2009; Philippe et al., 2009; Koifman et al., 2010; Abou Jamra et al., 2011; Kakar et al., 2012; Marangi et al., 2013; Giorgio et al., 2016; Abbasi et al., 2017; Duerinckx et al., 2018; Mortreux et al., 2018]. Our results are in line with these previous reports. There are shared characteristics between the cases in this report and the report of Krämer et al. [2021] in terms of ID, ASD symptoms, and ADHD except for microcephaly. Microcephaly is a clinical feature that has been reported in most patients with homozygous mutations in *TRAPPC9*. Krämer et al. [2021] reported that microcephaly and obesity may be developing as secondary in adolescence. This may be the reason for the variations in weight and head circumference sizes related to *TRAPPC9* mutations. However, the younger sibling in our report had the lower percentile of the head circumference.

Ke et al. [2020]reported that TRAPPC9 knock-out mice models presented postnatal delay in brain growth and enlargement of striatum related to imbalance of dopamine D1 and D2 neurons that can be contributors of ASD and schizophrenia [Langen et al., 2007; Emsley et al., 2015; Ke et al., 2020]. Also, pharmacological modulation of dopamine receptors with dopaminergic agents in mice improved results of behavioral tasks. The authors suggested that manipulation of the dopamine receptors may be useful for the treatment of *TRAPPC9* mutations associated with ID and behavioral problems. Several cases with *TRAPPC9* mutations had a diagnosis of ADHD. In this line, further studies investigating effects of dopaminergic agents used in ADHD medication on *TRAPPC9* mutations associated with behavioral problems would be beneficial for these cases. However, we had no opportunity to test these effects.

Wilton et al. [2020] demonstrated a map of *TRAPPC9* mutations; all reports originated from the Mediterranean area. Interestingly, our cases were the first report of the Turkish population in this region. Also, the authors suggested that children with absence of speech and intellectual disability with a consanguineous family history in the region of Mediterranean countries should be evaluated for *TRAPPC9* genetic testing. We suggest this evaluation also for the diagnosis of ASD and hand-flapping movements. Although the association between *TRAPPC9* mutations and diagnosis of ASD has been reported at low rates in the literature, this relationship has been emphasized more frequently in recent years [Krämer et al., 2021]. Even without a diagnosis of ASD, hand-flapping movements have often been reported. In addition, there are animal studies emphasizing the relationship of dopaminergic neurons with the diagnosis of ASD in TRAPPC9 knock-out mice models and detecting the positive behavioral effect of dopaminergic agents [Langen et al., 2007; Emsley et al., 2015; Ke et al., 2020]. This topic needs to be investigated in future studies.

Statement of Ethics

The protocols used in this study were in compliance with the Declaration of Helsinki and were approved by the Ethics Committee of the Fırat University (Protocol 19-5, December 12, 2019). Written informed consent was obtained from the parent/legal guardian of the patients for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

H.B., A.Ş., and S.C. provided genetic evaluation. G.Ü.B. and H.D. provided psychiatric and neurological evaluation. All authors designed the study. H.B. and G.Ü.B. wrote the manuscript.

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Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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