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Helsmoortel-Van der Aa syndrome in a 13-year-old girl with autistic spectrum disorder, dysmorphism, a right solitary kidney, and polycystic ovaries: a case report

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Abstract

Background Helsmoortel-Van der Aa syndrome was officially documented in 2014. Helsmoortel-Van der Aa syndrome is an extremely rare complex neurodegenerative disorder characterized by reduced intellectual capacity, motor dysfunction, facial dysmorphism, impaired development, and an increased predisposition to autism spectrum disorder. In addition, many patients also present with neuropsychiatric disorders, including attention deficit hyperactivity disorder, anxiety disorders, and various behavioral abnormalities. Helsmoortel-Van der Aa syndrome is challenging to identify solely on the basis of symptoms, and genetic investigations, including exome sequencing, may facilitate diagnosis.

Case presentation We report a case of 13-year-old Saudi patient who presented with dysmorphic features as illustrated in Fig. 1, severe mental retardation, autism spectrum disorder, and attention deficit hyperactivity disorder. Initial genetic testing was unremarkable; thus, a clinical exome analysis was performed to identify the genetic basis of the condition.

Conclusions Clinical exome analysis indicated an autosomal dominant Helsmoortel-Van der Aa syndrome with a likely pathogenic de novo variant within the activity-dependent neuroprotector homeobox (*ADNP*) gene not previously reported in Helsmoortel-Van der Aa syndrome. The patient had a right-sided solitary kidney and polycystic ovaries, conditions that were not previously associated with HVDAS.

Keywords *ADNP* gene, Case report, Facial dysmorphism, Helsmoortel-Van der Aa syndrome, Neurodevelopmental disorder

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Background

Helsmoortel-Van der Aa syndrome (HVDAS) is a relatively recently identified neurogenetic disorder documented in 2014 in ten people. It was identified by a group of scientists led by Helsmoortel *et al.*, who found that the condition occurred as a consequence of autosomal dominant de novo *ADNP* mutations (MIM #615873) [1]. HVDAS is characterized by intellectual and developmental delays in children and an increased predisposition to neurodevelopmental conditions such as autism spectrum disorder, along with facial dysmorphic features (a forehead with a high anterior hairline, blepharophimosis, palpebral ptosis, and hypertelorism), congenital heart defects, feeding problems, and hand and foot abnormalities [1].

The molecular basis of this syndrome is the haploinsufficiency of the *ADNP* gene (OMIM #611386). Pascolini *et al.* [2] reported the need for molecular analysis of *ADNP* when autism spectrum disorder (ASD) traits are observed in conjunction with facial dysmorphism in suspected cases of HVDAS. ADNP deficiency results in dysregulation of transcriptional [2] and p53-dependent cell apoptotic mechanisms [3–5]. In addition, ADNP deficiency in mice results in altered expression of genes associated with lipid metabolism [6], as well as cranial neural tube closure failure and subsequent death by embryonic day 9 [7]. There is a need to identify and characterize, at both symptom and genetic levels, cases of HVDAS, with a view to understanding the presentation of the disorder and genotype–phenotype relationships.

The present study reports a clinical case of a 13-year-old girl presenting with morphological/neurological symptoms associated with HVDAS, as well as novel features of right-sided solitary kidney and polycystic ovaries; she was found to possess a likely-pathogenic *ADNP* variant that has not been reported previously in HVDAS.

Case presentation

The 13-year-old Saudi girl was initially referred at the age of 10 years to the clinical genetic and metabolic disorder clinic in King Abdullah Specialist Children's Hospital, Riyadh, after presenting with dysmorphic features, severe mental retardation, ASD, and ADHD, according to the mental health professional clinic evaluation. In addition, she complained of sleep disturbances and frequent apnea attacks. The patient was a child of first-degree cousin Saudi parents and was born at term by emergency cesarean section after the pregnancy was complicated by preeclampsia. The patient had no significant perinatal history. The patient's early development was normal: she started sitting without support at 7 months and began walking at 12 months; however, she exhibited speech delay starting at the age of 3 years.

At our visit, her weight was 80 kg [>97th percentile, body mass index (BMI) of 40 indicative of morbid obesity], height was 132 cm (>2 SD below the mean), and head circumference of 52 cm (50th centile). Phenotypical examination revealed generalized hirsutism, prominent forehead, high anterior hairline, downslanted palpebral fissures, bilateral proptosis, hypertelorism, left iris coloboma, low-set ears, a smooth long philtrum, crowded teeth, and macroglossia. In addition, she had brachydactyly and a slight bilateral mallet finger deformity in her hands (Fig. 1). She also had joint laxity with recurrent ankle sprain accidents, episodes of left calcaneus, and distal fibula osteomyelitis.

The basic biochemistry and metabolic workups were unremarkable. A solitary right kidney and bilateral ovarian cysts were found on abdominal ultrasound. Brain magnetic resonance imaging only showed hypomyelination in the peritrigonal areas and other findings were unremarkable. Cardiac echocardiogram revealed trivial aortic, tricuspid, and mitral valve

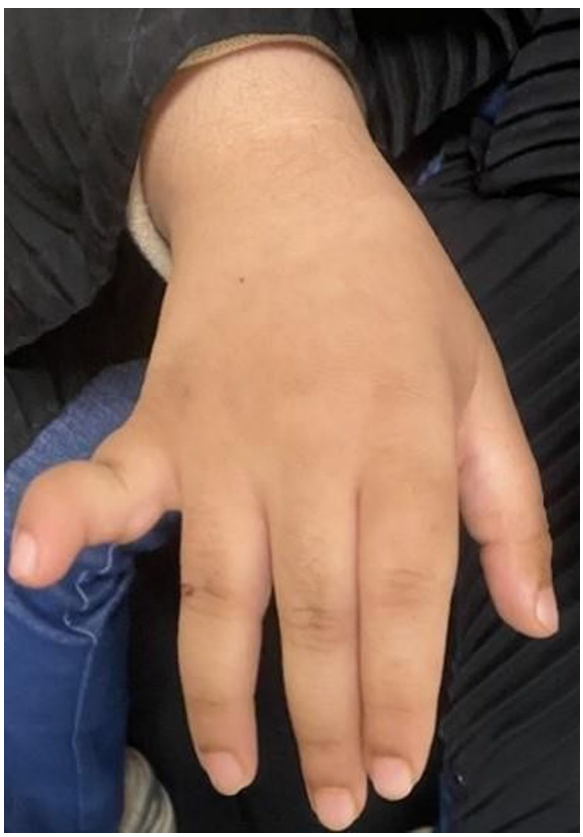

Fig. 1 The hand appearance of the proband. Note the brachydactyly and little-mallet finger deformity in the right hand (right), which were also seen in the left hand

insufficiency and closure by a secondary atrial septal defect. A Holter monitor connected for 24 hours revealed a predominant sinus rhythm and a first-degree atrioventricular block.

After informed consent was obtained, genetic studies were performed. The results of conventional chromosome analysis and a comparative genomic hybridization array (CGH) of peripheral lymphocytes were unremarkable. Conventional chromosome analysis was performed using the standard Giemsa banding using trypsin with Wright's stain and karyotype by Leica CytoVision imaging (Leica, Biosystems). The CGH was done using Affymetrix CytoScan HD array platform which contains ~2.7 million markers, including 750,000 SNP markers, across the whole genome covering 96% of the genes. The data were analyzed using the Affymetrix Chromosome Analysis Suite (ChAS) version 4.2.1 and interpreted on the basis of the Genome Reference Consortium Human Build38 [GRCh38].

Therefore, we performed a clinical exome analysis to determine the genetic basis of the condition. It was performed using manufacturing protocol instructions in which a DNA capture against approximately 41 Mb of the human coding exome (targeting > 98% of the coding RefSeq from the human genome build (GRCh37/hg19) are used to enrich target regions from fragmented genomic DNA with the Twist Human Core Exome Plus kit. The generated library is sequenced on an Illumina platform to obtain at least 20× coverage depth for > 98% of the targeted bases. All disease-causing variants were checked against the Human Gene Mutation Database (HGMD), ClinVar, the Genome Aggregation Database (gnomAD), and the Exome Aggregation Consortium (ExAC), using the in silico tools such as SIFT (http://sift.jcvi.org/), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), and Mutation Taster (http://www.mutationtaster.org) to predict variant coding effects on protein function. The result showed a heterozygous likely pathogenic variant in the *ADNP* gene c.1265dup p. (Gln423Serf*17), creating a shift in the reading frame starting at codon 423. The new reading frame ended in stop codon 16, positioned downstream, consistent with the genetic diagnosis of autosomal-dominant HVDAS. Clinical exome analysis confirmed the presence of the variant in the proband and its absence in her parents, supporting its de novo nature. The variant was also confirmed by Sanger sequencing using specific designed bidirectional primers and Big Dye Terminator v. 3.1 cycle sequencing kit (Applied Biosystems, Foster City, CA, USA) on Genetic Analyzer 3500 instrument (Thermofisher Scientific, USA).

Discussion and conclusions

Autosomal dominant de novo mutations in *ADNP* (MIM #615873) are a prominent pathogenic mechanism underlying HVDAS syndrome development, and variants within this gene may explain around 1 in 500 cases of idiopathic autism spectrum disorder [1], thought to affect around 1 in 59 children overall [8]. Extensive sequencing capabilities allow us to identify and understand the causes of neurodevelopmental disorders more accurately by assembling a genetic library. Genetic variation in the *ADNP* homeobox gene can lead to the development of syndromic autism, exacerbating behavioral problems in approximately 78% of cases. There is limited evidence that behavioral symptoms in individuals with ADNP variants and autism might be managed with antipsychotic (risperidone) medication [8]. However, there is a need for further research into the pharmacological management of neurogenetic conditions such as HVDAS with a view to optimizing treatment.

Patients with *ADNP* disorders represent complex clinical cases due to the multifaceted nature of symptoms arising directly from dysregulation of transcriptional and other biochemical pathways. In addition, there are likely other secondary abnormalities that result in mental and motor delays, and abnormalities of the body and facial structure [2]. Global developmental delay, difficulty eating, and regular cyanosis are additional signs of HVDAS [9]. In addition, mood disorders combined with attention deficit/hyperactivity disorder appear to be direct consequences of children's mental and motor retardation at an early age.

It should be noted that there can be considerable variability in the presentation of neurological and physiological symptoms in individuals with *ADNP* variants (including de novo variants), making the diagnosis and detection of HVDAS challenging. The Deciphering Developmental Disorders Study (2015) reported clinical findings in four cases with similar features, all of which had moderate general mental retardation. Almost all cases were accompanied by visual limb abnormalities and abnormalities related to primary and general metabolism. Furthermore, two patients had plagiocephaly and hair disorders. In a worldwide cohort of patients with HVDAS, 78 were under 40 years of age, 73% of whom were diagnosed with mental retardation [10]. On average, delayed speech and motor development were seen in 70.5% individuals, conduct disorder in 48%, and hypotonic conditions in 54% patients. In addition, eating disorders and gastrointestinal problems were present in most patients (60% individuals) [10].

The development of *ADNP*-associated syndromes can be observed at an early age. Shillington *et al.* [8] reported on an 18-month-old female patient with a de novo pathogenic *ADNP* variant presenting initially with a congenital diaphragmatic hernia and later (3 years) with features of autism. The patient also had global developmental delay, early tooth formation, and vision problems. In addition, the patient was unresponsive to behavioral treatment, and a congenital heart defect aggravated her feeding, breathing, and motor activity.

Abnormalities in genome-wide DNA methylation in blood samples from 22 individuals with *ADNP* variants were identified in a study by Bend *et al.*, and the syndrome might be reconceptualized as a systemic epigenetic disorder [12]; the nature of these epigenetic changes could be classified depending upon the location of the *ADNP* variant (one of two locations). This finding has since been replicated in 24 patients with HVDAS [11]. In the latter study, no association was found between the clinical presentation of the two groups, nor between the extent of DNA methylation disturbances and disorder severity. These data suggest that further research into the relationship between variant position (including the novel variant implicated here), genome-wide methylation patterns, and symptomatology is required. Moreover, they suggest the possibility of using methylation tools or associated therapies to achieve behavioral function modification in future.

Unusual manifestations of *ADNP* abnormalities include dental lesions, demineralization of the enamel, and detection of dark stains on the enamel, which were documented in a 9-year-old boy who also had lower oral mucocele [13]. However, there is currently no proven relationship between dental lesions and *ADNP* syndrome, and it is impossible to obtain conclusive results from a single case.

Our patient demonstrated the clinical and molecular phenotype of HVDAS but also had a right solitary kidney and polycystic ovaries, which have not previously been mentioned in the literature. In addition, our patient had significant congenital heart anomalies—which are uncommon in this disease—with a second-order atrial septal defect requiring surgery and device closure, which has also not been previously reported. We found that the putative causative genetic variant was a de novo frameshift mutation, c.1265dup p. (Gln423Serf*17), creating a frameshift starting at codon 423. The new reading frame ended with stop codon 16 located downstream, and this variant has not been reported in HVDAS. Potentially, renal abnormalities and polycystic ovarian disease may be specifically associated with this variant of HVDAS, or they may be a more general, but underreported finding, across all HVDAS cases. Our work supports the idea that molecular analysis of the *ADNP* gene should be considered when autism spectrum disorder (ASD) traits and behavioral disorder facial dysmorphism are observed. We have encountered no limitations in the study.

Abbreviations

ASD	Autism spectrum disorder
HVDAS	Helsmoortel-Van der Aa Syndrome
ADNP	Activity-dependent neuroprotector homeobox
ADHD	Attention deficit hyperactivity disorder

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Author contributions
The manuscript was primarily written by EAE, MA, KAE and MAB and the editing was supervised by WD. In addition, WE diagnosed and evaluated the patient during the follow-up period. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
The case report was reviewed and approved by the institutional review board committee of King Abdullah International Medical Research Centre with reference number RYD-23-419812-11537. The consent to participate in the study and the publication of photographs was obtained from the patient's guardian.

Consent for publication
Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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