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Case Report

Patient with Helsmoortel-van der Aa Syndrome and O'Donnell-Luria-Rodan Syndrome: a case report

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Abstract: Heterozygous pathogenic variants in the ADNP gene cause Helsmoortel-van der Aa syndrome which is an autosomal dominant mutation, whose patients have autism spectrum disorder (ASD) and intellectual disability. Pathogenic variants in the KTM2E gene are related to O'Donnell-Luria-Rodan syndrome, also autosomal dominant, characterized by global development delay. The case of a male patient, only child, born at term measuring 45 cm (z-1) and weighing 2.460 kg (z-2) was described. The patient presented short stature, autism spectrum disorder, delay in neuropsychomotor development, gastrointestinal reflux, hyperopia, recurrent infections, and constipation. The result from whole exome sequencing (WES) identified two variants of uncertain significance (VUS) in the ADNP and KMT2E genes, whose syndrome related in literature have compatible signs and symptoms with those found in the patient.

Keywords: Helsmoortel-van der Aa Syndrome; HVDAS; O'Donnell-Luria-Rodan Syndrome; ODLURO.

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1. Introduction

Neurodevelopmental disorders (NDDs) are neurological dysfunctions that can cause attention, memory, perception, speech, resolution, and social interaction problems. Among them, there are autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), epilepsy, intellectual disability, and rare genetic syndromes. Next-generation sequencing (NGS) has allowed several genes and genetic mutations related to brain development to be detected and their roles investigated [1-3].

ADNP (Activity Dependent Neuroprotector Homeobox) mutations are described as one of the most frequent genetic causes of autism and intellectual disability, being mutated in about 0,17% of all cases. ADNP gene is located on the long arm of chromosome 20 (20q13.13) and encodes the activity-dependent neuroprotective protein, which is prevalently expressed in the brain and plays an essential role in neurodevelopment, neuroprotection, axonal transport, and spinal dendritic formation. Patients with heterozygous pathogenic variants develop the Helsmoortel-van der Aa syndrome (HVDAS), which segregates with an autosomal dominant inheritance pattern and has a prevalence of 1 in 100.000 individuals [4-6]. The main signs and symptoms include moderate to severe intellectual disability, neuropsychomotor delay, ASD, gastrointestinal, skeletal, and behavioral impairments, recurrent infections, hypotonia, and insomnia [4, 7-8].

Heterozygous mutations in the *KMT2E* (lysine n-methyltransferase 2E) gene are related to O'Donnell-Luria-Rodan syndrome (ODLURO), which segregates with an autosomal dominant inheritance pattern [9]. *KMT2E* gene is located on the long arm of chromosome 7 (7q22.3) and encodes a functional protein belonging to lysine n-methyltransferase 2 (KMT2) family, with function related to the regulation of transcription factors by binding to the methylated histones H3K4me2 and H3K4me3, playing a role on the cortex development in the fetus and may have a behavioral influence [10]. The main clinical features of affected individuals are neurodevelopmental delay, facial dysmorphia, macrocephaly, epilepsy, speech delay, memory dysfunction, ASD, ADHD, hypotonia, and seizures [9, 11-12].

Both syndromes were discovered in the last 10 years: 2014 for Helsmoortel-van der Aa syndrome and 2019 for ODLURO syndrome. New variants and genetic mechanisms are still being investigated for complete elucidation of the reported cases [7, 11]. The aim of the study is to describe a rare case of a male pediatric patient that has two variants of uncertain significance (VUS) in the *ADNP* and *KMT2E* genes. So far, we did not identify case reports in the scientific literature that describe these genetic syndromes occurring concurrently in a patient.

2. Case Report

A male patient, only child, born to non-consanguineous parents measuring 45cm (z-1) and weighing 2.460kg (z-2). His mother had a high-risk prenatal, being subjected to bariatric surgery before getting pregnant. During pregnancy, she suffered from frequent vomits and was diagnosed with hyperemesis gravidarum. During prenatal care, a morphological ultrasound was requested, in which were noticed alterations in the size of the femur and an abnormal length of superior and inferior limbs of the fetus, suspecting achondroplasia. Caesarian delivery at term with 38 weeks due to a decrease in the amniotic fluid.

In the first years, the family noticed walking and speech delay, phonophobia and hyperfocus, besides some suspicious behaviors such as playing only with the wheels of cars, being highly selective to food, and aggressive episodes. At one year of age, it was observed a displacement of the plane and short stature, proceeding with an orthopedic evaluation being diagnosed with genu varum (Figure 1).

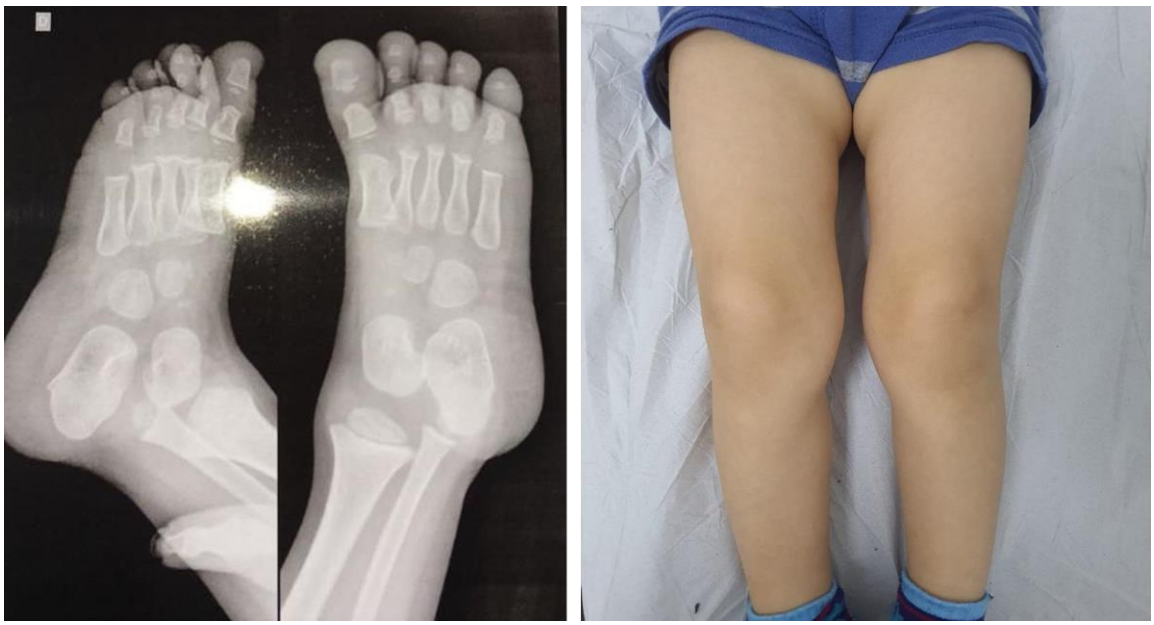

Figure 1: Feet x-ray showing shortening of the feet bones (left image – 21.01.2021) and a picture of genu varum (right image – 14.02.2023).

In 2021, the patient was evaluated by a multi-professional team composed of a psychologist, psychiatrist, occupational therapist, and physiotherapist. After neurological evaluations, the team care confirmed the suspected diagnosis of global development delay and autism spectrum disorder. On the ophthalmological evaluation, it was also noticed hypermetropia. Due to all these signs and symptoms, it was requested a whole exome sequencing (WES) to investigate possible genetic causes. Other genetic tests such as karyotype, fragile-X test and microarray were not performed. The exome's result is shown in table 1.

Table 1: Result of whole exome sequencing accomplished in 10.20.2021.

Genes	**ADNP**	**KMT2E**
Nomenclature	Chr20(GRCh37): g49510204C>G NM_00128253.2: c.1147G>C p. (Glu383Gln) Exon 6	Chr7(GRCh37): g.104717489G>A NM_182931.2: c.848G>A p. (Arg283Gln) Exon 10
Zygosity and Depth	HT / 106x	HT / 90x
VAF	48%	46%
Type	*Missense*	*Missense*
Conservation	High	High
Population frequency	<0,001%	0,001%
Classification	VUS	VUS
Syndrome and inheritance pattern	Helsmoortel-van der Aa Syndrome, autosomal dominant	O'Donnell-Luria-Rodan Syndrome, autosomal dominant

Subtitle = HT: heterozygous; VAF: variant allele frequency; OMIM: Online Mendelian Inheritance in Man; VUS: variant of uncertain significance.

The genetic test reported two VUS on the ADNP and KMT2E genes. No other VUS or pathogenic variants were found. The genetic counseling team made, then, a closer evaluation of the patient's signs and symptoms, which could be framed in those observed in the Helsmoortel-van der Aa (related to ADNP) and O'Donnell-Luria-Rodan syndromes (related to KMT2E) (Table 2).

Table 2: Signs and symptoms observed in the patient that frame in those observed in the Helsmoortel-van der Aa (ADNP) and O'Donnell-Luria-Rodan (KMT2E) syndromes.

Helsmoortel-van der Aa syndrome symptoms	**Frequency (%)**	**O'Donnell-Luria-Rodan syndrome symptoms**	**Frequency (%)**
Global development delay	100	Speech development delay	83
Speech development delay	99	Intellectual disability	72
ASD	93	Motor delay	69
Social difficulty	89	High-sized forehead	59
Gastroesophageal reflux	83	Muscle hypotonia	51
Sudden changes in behaviour	78	Sleep problems	47
Cortical development abnormalities	62	ASD	31
Muscle hypotonia	55	Bowel constipation	29
Anxiety	54	Stereotypes	17
Recurrent infeccions	51	Vomits	9
Bowel constipation	49	Gastroesophageal reflux	7

Fingers abnormalities	46	ADHD	6
ADHD	44	Dysmorphic facial features	6
Hyperopia	40	Aggressive behavior	6
Urinary incontinence	28	Abusive behavior	6

Note: Frequency data obtained in references 4, 8, 10 and 13.

In the evaluations carried out by the multi-professional team care between 2021 and 2023, it was noticed a learning and feeding difficulty, global development delay, speech delay, ambulation difficulty, gastroesophageal reflux, frequent vomits, ogival palate, incisors protrusion, bowel constipation, phimosis, weak muscles, genu varum, asymmetry of knees and ankles in the range of 0.5cm, cracked, scaly, fragile and brittle nails on hands and feet, significant weight loss and use of glasses to correct hypermetropia and astigmatism. He was hospitalized in March 2021 with fever and acute respiratory distress. It was reported repetitive pneumonias that got worse after contracting COVID in october 2020, but he recovered successfully.

At the moment, the patient is alive and being followed-up only by the pediatrician and the neuropediatrician services for assistance in the muscular hypotonia and regurgitation. It was emphasized to the patient's family that a multi-professional treatment, including a psychological follow-up, will be necessary to improve his intellectual development and quality of life.

3. Discussion and conclusion

In the Helsmoortel-van-der Aa syndrome, a certain diagnosis is related to ADNP variants that cause loss of protein function, which are in general nonsense or frameshift mutations in the 3' end of exon 5 and generate truncated proteins that escape from Nonsense-Mediated Decay system (NMD) [4, 5]. In the last years, patients presenting pathogenic variants in the ADNP gene have been more studied due to the influence of the gene in ASD [13]. Although case reports describing this syndrome are still scarce, most of them describe HVDAS patients with signs and symptoms similar to those found in our patient: behavioral problems, autism spectrum, dysmorphic craniofacial features, constipation, global development delay and hypotonia [14-17].

A few patients may have particular features that are not very common, such as the congenital heart defect case described by Chen and colleagues [14]. On the other hand, other cases may not have some typical features, such as the patient described by Li and colleagues [15], who did not present ASD and social problems. All of the variants found in the cases quoted above were nonsense or frameshift, except for the case reported by Li [15], who showed a heterozygous interstitial deletion of 63 kb in the chromosomal region 20q13.13, containing the ADNP and DPM1 genes.

According to the criterion established by the American College of Medical Genetics (ACMG), the c.1147G>C p.Gly383Gln missense mutation is currently classified as a variant of uncertain significance (VUS), having an extremely low frequency in populational databases as a moderate pathogenic support criterion (PMS). There are no articles in the literature that describe clinical cases with this variant and the partial scores of predictors aggregated by Franklin tool (Revel, SIFT, Polyphen 2, Varity) classify this variant as VUS (https://franklin.genoox.com/clinical-db/variant/snp/chr20-49510104-C-G). According to Cappuyns and colleagues [13], mutations at the N-terminus at residue 1–412 (the variant found here is at residue 383) are shown to negatively impact ADNP expression through cytosolic proteasomal degradation, but these variant lacks enough data to support a reclassification (Figure 2).

In ODLURO syndrome, the rarity of case reports is more pronounced than HVDAS since it was first described only in 2019. Most part of the data we have about ODLURO come from two cohorts made by O'Donnell-Luria et al. [18] and Velmans et al. [10],

totalizing 56 patients that had their variants identified. A considerable number of both cohorts have signs and symptoms described in our patient: development and speech delay, autistic traits, constipation, broad forehead and hypotonia [10, 18-20].

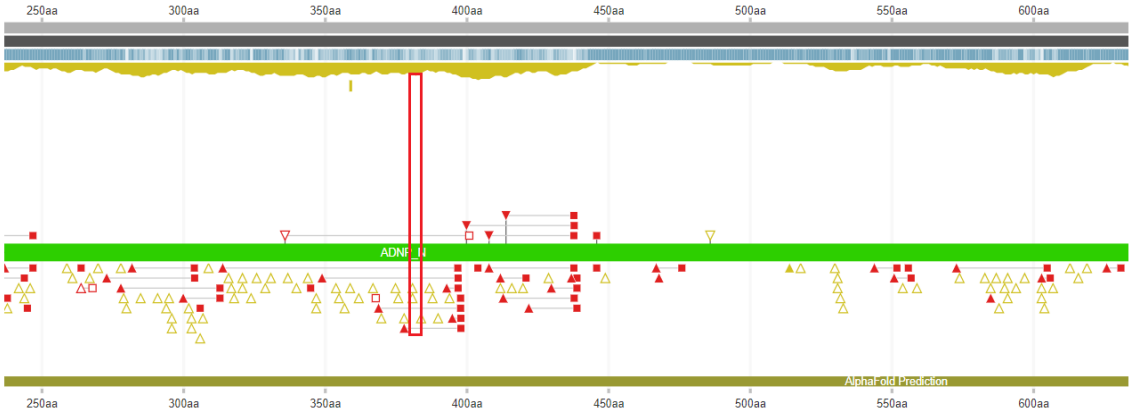

Figure 2: Region where the ADNP:c.1147G>C (p.Glu383Gln) variant is found. Note: the image above was obtained in the Decipher Genomics v11.21 software (https://www.deciphergenomics.org/). It is showing part of the ADNP region based on the MANE select (the most biologically relevant transcript), its domain (in green) and variants (triangles and squares) that are described in ClinVar. The c.1147G>C variant is not described, so the red mark is an approximate region generated using the location of nearby variants.

Most of the cases showed de novo variants that are distributed along the KMT2E gene, which can be single nucleotide variations (SNV), indels or copy number variations (CNV) [21] Frameshift and nonsense mutations are common, but missense and splicing variants have already been reported and are related to more evident and severe clinical phenotypes [9, 11, 12, 22]. Furthermore, some cases indicate the possibility of incomplete penetrance and variable expressivity. The patient described by Cătană and colleagues [21] has the heterozygous deletion c.498-11T>C currently classified as VUS and some typical features found in our patient, such as behavioral problems and gastroesophageal reflux. His father, also a carrier of this variant, presents only less severe psychiatric symptoms.

The ACMG support criterion for the c.848G>A missense variant is the same found in the ADNP gene. No previous articles have described this variant, except from the recent submission made by Invitae on ClinVar in a patient whose condition was not provided. The laboratory performed what they described as an "advanced modeling of protein sequence and biophysical properties", that includes structural, functional, and spatial information, amino acid conservation, physicochemical variation, residue mobility, and thermodynamic stability. The results indicated that the variant is not expected to disrupt KMT2E protein function, but the available evidence is insufficient to determine its role in ODLURO. Franklin's classification is also VUS (https://franklin.genoox.com/clinical-db/variant/snp/chr7-104717489-G-A).

This variant is found at the beginning of the SET domain, which is an enzymatic domain predicted to be inactive; on the other hand, SET domain is highly conserved, and some studies have proposed that it might have a role on H3K4 methylation through transcriptional regulation of additional histone-modifying enzymes (Figure 3) [18]. New case reports are being published and more de novo variants are being discovered, but as the case described by Cătană et al. [21] and Kosma et al. [20] (that revealed a 239-kb deletion encompassing the genomic region 7q22.2q22.3 classified as VUS) and our team, a resolution of the challenge regarding which impact these VUS could have in the clinical decisions remains unclear.

With the introduction of multigene panels and whole exome and genome sequencing, the number of identified variants per person has increased progressively; in parallel, the detection of VUS has expanded. These variants are communicated to the patients and their relatives; however, it does not have a clinical value to guide medical decisions definitively or indicate the necessity of performing predictive tests on family members [23, 24]. Therefore, an improvement in VUS classification techniques must be made in the clinical setting, altogether with a greater collection of populational data (especially in underrepresented and reported populations in national databases such as ABraOM), in addition to a decrease in the cost of familiar testing [25].

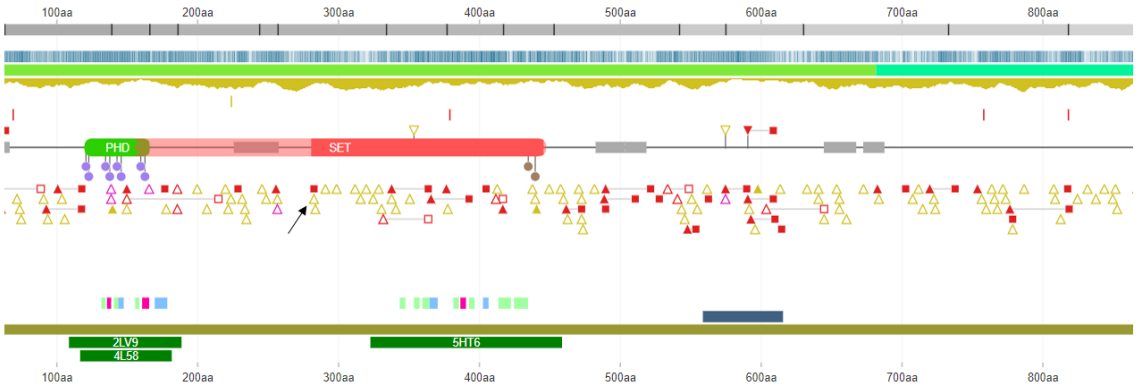

Figure 3: Region where the KMT2E:c.848G>A (p.Arg283Gln) variant is found. Note: the image above was also obtained in the Decipher Genomics v11.21 software. The black arrow indicates the region where the c.848G>A variant is found in the KMT2E gene based on the MANE select.

The reported case has a clinical diagnosis of Helsmoortel-van der Aa syndrome and O'Donnell-Luria-Rodan syndrome, being the first report to describe two potential variants of causing disease in ADNP and KMT2E genes occurring concurrently. Although the performed exome reported variants of uncertain significance, the signs and symptoms of the patient described in this paper are compatible with those found in carriers of these two syndromes, as shown in chart 1. Furthermore, the two VUS found in the patient lacks enough information regarding the exact populational frequency and protein effect. We would also like to highlight that no populational frequency data of these variants in Brazil are available, probably because the case reported here is the first occurrence of them described in the country.

A test of familiar co-segregation would be interesting because if one of the parents (clinically healthy) showed the same variants found in the child, it could be inferred whether the patient's phenotype is related to the variants found in his exome or not. However, these genetic syndromes cannot be cured, and the multi-professional follow-up indicated for our patient included genetic counseling, occupational therapy, and medical, psychological, and educational support to improve his quality of life [26]. We expect that, in the future, more studies and VUS reclassification techniques be developed to ensure a definitive diagnosis for the carriers of these variants.

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Conflicts of Interest: None.

Supplementary Materials: None.

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