O'Donnel-Luria-Rodan Syndrome: New gene variant identified in Romania (A case report)

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Abstract. O'Donnel-Luria-Rodan (ODLURO) syndrome is a neurodevelopmental disorder with autosomal dominant inheritance. It appears more frequently in males during the first decade of life and is associated with developmental delay, low intelligence quotient, autism spectrum disorder-like behavior, epilepsy, speech delay, aggression, facial and skeletal deformities, gastrointestinal symptoms and hypotonia. Although few cases have been documented, it appears that the phenotype spectrum may vary, especially between the two biological sexes. The present study reported a case of a 5-year-old male patient who was diagnosed with ODLURO at the age of 4 years using whole-exome sequencing. Molecular analysis identified a new mutation in the lysine methyltransferase 2E (inactive) (KMT2E) gene, which was classified as a variant with unknown significance. The father, who presented with non-specific and undiagnosed psychiatric manifestations, presented the same KMT2E variant. The case described in the present study is not only interesting because there are <40 cases described in the literature, but also because a new inherited mutation in the KMT2E gene, present in both father and son, that resulted in different phenotypic manifestations was identified.

Introduction

O'Donnel-Luria-Rodan (ODLURO) syndrome was first reported in 2019 in 30 patients, with the majority of patients being under the age of 10 years. To date, there have been 38 reported cases worldwide (1). It is a neurodevelopmental disorder that leads to delayed development, low intelligence quotient (IQ), speech delay, autism spectrum disorders, anxiety and seizures. Other manifestations include hypotonia, feeding difficulties and mild physical deformities (2). The inheritance of ODLURO is autosomal dominant, although the majority of cases appear de novo (3). The clinical manifestations develop at an early age and tend to have variable expressivity that is primarily dependent on the biological sex of the patient (4).

The lysine methyltransferase 2E (inactive) (KMT2E) gene encodes a member of the lysine N-methyltransferase-2 family, a group of enzymes that serve an important role in chromatin remodeling through transcriptional regulation. ODLURO is caused by mutations in the KMT2E gene that result in pathogenic enzyme variants responsible for regulating histone 4 methylation on lysine 3 (H3K4). Lack of proper methylation leads to abnormalities in the molecular activity of neurons. As methylation maintains the open chromatin state, any dysregulation affects proper transcription regulation. H3K4 methylation undergoes dynamic changes during the neurodevelopmental phase, impacting both the environment of neural and glial cells in the brain and the molecular activity of the neurons (5,6).

O'Donnell-Luria identified 31 different mutations in the heterozygous state for the KMT2E gene in a group of 34 individuals with ODLURO syndrome (OMIM 618512) (4). All patients received clinical and molecular evaluation via exome or genome sequencing through a collaboration of four research centers. The majority of the identified mutations were consistent with haploinsufficiency due to truncated proteins, except four patients with missense mutations affecting highly conserved residues. As expected, the majority of the mutations occurred de novo, dominant variant inheritance was observed in three affected siblings who may have inherited the variant from the affected father. Functional studies of the identified variants were not performed, but the authors speculated that the pathogenic mechanism linked to altered KMT2E binding function was the result of haploinsufficiency.

Case report

The present study reports the case of a 5-year-old male patient diagnosed with ODLURO syndrome at the age of 4 years, who was the first reported patient with ODLURO in Romania. The
ODLURO is a newly defined genetic condition, and as with most rare genetic diseases, there is little information in the literature on its etiopathogenesis. The authors who defined this most rare genetic diseases, there is little information in the literature on its etiopathogenesis. The authors who defined this syndrome revealed an association between KMT2E gene mutations and a clinical phenotype with several common elements, including neurodevelopmental delay with autistic behavior and intellectual disability, non-specific facial dysmorphia and various functional abnormalities (4).

The patient reported in the present study was a 5-year-old male who was diagnosed with ODLURO based on clinical manifestations and a heterozygous mutation in the KMT2E gene (KMT2E NM_018682.3: c.498-11T>C), which is currently classified as a variant of uncertain significance (VUS) due to the lack of reported cases with this genetic variant in the medical literature related to ODLURO. The same variant was identified in the patient's father, who also presented with psychiatric symptoms, but not to the same severity as the patient. In this case, VUS management and evaluating a possible etiopathogenic link with the phenotype was challenging. The label VUS emerges if no reports connect the variant to the specific disease. Also, if a variant is extremely rare, it might take time to conduct comprehensive studies and catalog enough cases that associate it with a medical condition. The arguments that the identified variant may be pathogenic are due to its molecular characteristics; According to the investigator, *in silico* analysis shows that the mutation is predicted to disrupt the highly conserved acceptor splice site and thus may have a negative effect on the phenotype, as it alters the AG-3' intronic acceptor site, with the synthesis of an incomplete mRNA and defective unstable polypeptide synthesis (7).

Although the majority of cases of ODLURO are a consequence of a de novo mutation, inheritance was identified in a family with three affected siblings (8) Parenteral WES analysis identified the same variant in the father. Interestingly, the father presented with autistic-like behavior and his wife stated that he has a childhood history for a psychiatric disorder, but could not provide details related to the diagnosis. Phenotypic differences may be explained by incomplete penetrance and variable expressivity, an already well-known aspect for dominant inheritance (9).

Autism spectrum disorder is common in patients with ODLURO, especially in males, together with speech delay, intellectual disability, anxiety and aggressive behavior (8). The KMT2E gene is known to serve an important role in neurodevelopment, and mutations in this gene have been linked to several cases of epilepsy, autism spectrum disorder, intellectual disability and schizophrenia (10). The patient described in the present study also presented a complete lack of verbal communication, as well as delayed speech.

Facial dysmorphic features like dolichocephaly, large forehead, deep-set eyes, antimongoloid palpebral fissures, periorbital fullness, prominent cheeks and prominent nasolabial folds have been described in patients with ODLURO (11). The patient described in the present study presented with macrocephaly, frontal bossing, antimongoloid palpebral fissures, prominent cheeks and prominent nasolabial folds.

Gastrointestinal symptoms have also been reported in numerous patients with ODLURO (4). However, predisposition to developing coeliac disease and being positive for HLA DQ 2.5 have not yet been reported in correlation with ODLURO, and might be independent traits. Although eating disorders, such as compulsive overeating, have not previously been reported to be linked to ODLURO, the patient reported...
In the present study required nutritional and psychological guidance for this condition to restore proper nutritional values.

In conclusion, based on the aforementioned genetic findings and taking into consideration the phenotype of the patient, the c.498-11T>C, KMT2E VUS was a potential cause for the patient's symptoms. However, further studies are required to confirm the pathogenicity of the variant. It appeared that the mutation was inherited from the father and decreased penetrance may explain the milder phenotype, restricted to autistic-like behavior, therefore further functional and clinical studies are necessary and will allow precise pinpointing of the pathologic significance of this variant. The case reported in the present study should remain in focus as the first case of ODLURO diagnosed in Romania.

ODLURO is a rare neurodevelopmental disorder caused by a germline mutation in the KMT2E gene that is primarily de novo, but also inheritable. Common symptoms include delayed development, low IQ, poor verbal communication, autism spectrum disorders, anxiety and seizures. Other manifestations include hypotonia, feeding difficulties and mild physical deformities. The present study reported a 5-year-old male patient who presented with macrocephaly and mild facial dysmorphia, including antimongoloid slanting palpebral fissures, prominent nasolabial folds and frontal bossing, tapering fingers, and severe gastroesophageal reflux with recurrent nausea, vomiting and abdominal pain in association with KMT2E NM_018682.3: c.498-11T>C, heterozygous variant, with gluten intolerance as an atypical finding.

### Table I. Clinical features of the presented patient in comparison with other reported patients with ODLURO syndrome (12-14).

| Clinical features in ODLURO syndrome | Manifestations in previously reported cases | Manifestations in the presented case |
|-------------------------------------|---------------------------------------------|-------------------------------------|
| Facial dysmorphic features          | Dolichocephaly, large forehead, deep-set eyes, antimongoloid palpebral fissures, periorbital fullness, prominent cheeks and prominent nasolabial folds | Macrocephaly, frontal bossing, antimongoloid palpebral fissures, prominent cheeks and prominent nasolabial folds |
| Height, weight, and developmental abnormalities | Short stature and delayed development | Delayed physical development |
| Ostearticular abnormalities         | Tapering fingers | Tapering fingers |
| Neurological and psychiatric involvement | Hypotonia, seizures, intellectual disability, delayed speech, anxiety and autism | Autism, intellectual disability, lack of verbal communication, anxiety and eating disorders |
| Cardiovascular involvement          | Septal defects | N/A |
| Gastroenterological involvement     | Nausea, vomiting, motility disorder and gastroesophageal reflux | Nausea, vomiting, motility disorder and gastroesophageal reflux |
| Immunological involvement           | N/A | Positive for HLA DQ 2.5, which results in a predisposition to developing celiac disease |

ODLURO, O'Donnell-Luria-Rodan.

Figure 1. Facial phenotype and tapering fingers. (A and C) Facial phenotype of the patient with dolichocephaly, prominent forehead and antimongoloid palpebral fissures. (B) Tapering fingers of the patient.
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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AC and MSM conducted the genetic consult and counselling. AC, ZCB, EK, DM and II interpreted the genetic test results and confirmed the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient's family provided consent for publication.

Competing interests

The authors declare that they have no competing interests.

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