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

ANDREEA CĂTANĂ[1-3], ENIKŐ KUTASI[1], ZINA CUZMICI-BARABAȘ[2,3], DIANA MILITARU[2], IRINA IORDĂNESCU[3] and MARIELA SANDA MILITARU[2,3]

[1]Department of Oncogenetics, Institute of Oncology I. Chiricuță, Cluj-Napoca, Transylvania 4000015; [2]Department of Molecular Sciences, University of Medicine and Pharmacy, Cluj-Napoca, Transylvania 4000012; [3]Department of Medical Genetics, Genetic Center Laboratory, Regina Maria, Bucharest 011376, Romania

Received October 1, 2021; Accepted November 1, 2021

DOI: 10.3892/etm.2022.11294

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

Correspondence to: Dr Andreea Cătană, Department of Oncogenetics, Institute of Oncology I. Chiricuță, 34-36 Str. Republicii, Cluj-Napoca, Transylvania 4000015, Romania
E-mail: catanaandreea@gmail.com

Key words: O'Donnel-Luria-Rodan syndrome, lysine methyltransferase 2E (inactive), variant of uncertain significance, autism spectrum disorder, molecular analysis

patient was the only child of non-consanguineous parents and the family history was negative. The patient was born at term after an uncomplicated pregnancy and delivery, and displayed normal parameters at birth.

Gross motor development was delayed, as the patient began sitting at 7 months and walking at 15 months of age. Verbal skill communication was never acquired and the mother noticed behavioral anomalies, including avoidance of gaze, retreating into repetitive, self-centered games, and no interaction with other children of his age. After the age of 2 years, the patient was consulted by several pediatric neurologists and psychiatrists, but in the absence of specific magnetic resonance imaging anatomical and electrophysiological functional abnormalities of the CNS, the patient was diagnosed with an idiopathic autistic spectrum disorder. At the age of 5 years, the patient was referred for medical genetic assessment. Overall development showed the-standard deviation values of height and weight for the age. The patient recognized only a few basic, short words, but could not reproduce them or verbally communicate in any way. The patient's father also faced challenges with social interactions, living isolated from the family and displaying autistic behaviors, but had not undergone a psychological evaluation.

Intellectual disability was objectified by the psychologist using specific evaluation tools, and the patient presented with an IQ of 52. The patient also displayed the following characteristics: Self-isolation, repetitive and unusual body movements, paroxysmal crying, reduced attention span to 6-7 sec and difficulty making eye contact. All of these, in addition with the presentations of anxiety and a tendency to self-harm indicated an autism spectrum disorder.

The patient had light, sensitive skin, blonde hair, blue eyes, and presented macrocephaly and mild facial dysmorphia, including antimongoloid slanting palpebral fissures, prominent nasolabial folds and frontal bossing. Another interesting finding was the narrowing of the distal phalanx of the patient's fingers (Fig. 1).

Among the most debilitating symptoms, severe gastroesophageal reflux with recurrent nausea, vomiting and abdominal pain was reported. Nutrigenomic testing was recommended, and the results revealed a tendency for compulsive eating behaviors, especially for calorie-rich foods. Moreover, the specific HLA DQ 2.5 haplotype defines a predisposition to developing celiac disease due to gluten intolerance.

Due to the heterogeneous, non-specific clinical manifestations, whole-exome sequencing (WES) was performed with parental informed consent. The investigator reported a heterozygous mutation in the KMT2E gene (KMT2E NM_018682.3: c.498-11T>C), which was characterized by a deletion that resulted in the inclusion of a pathogenic exon in the mature mRNA, thus altering the structure and function of the synthesized polypeptide. Targeted genetic testing was performed in both parents, and the variant was identified in the father (Table I).

Discussion

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 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 etiopatogenic 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) Parental 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

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
Osteoarticular 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'Donnel-Luria-Rodan.

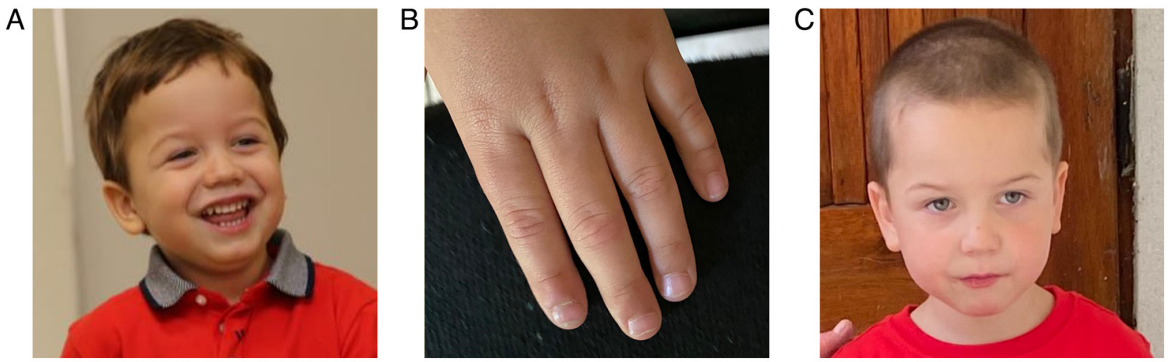

Figure 1. Facial phenotype and tapering fingers. (A and C) Facial phenotype of the patient with dolichocephaly, prominent forehead and antimongoloid palpebral fissures. (B) Tapering fingers of the patient.

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 is an example of rare disease challenges for diagnostic uncertainty when considering the unknown clinical significance of a specific variant. Until further evidence for the identified variant has been identified, 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.

Acknowledgements

Not applicable.

Funding

No funding was received.

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.

References

1. Omim.org: OMIM Entry-# 618512- O'Donell-Luria-Rodan Syndrome; ODLURO. https://www.omim.org/entry/618512> Accessed August 3, 2021.
2. Velmans C, O'Donnell-Luria AH, Argilli E, Tran Mau-Them F, Vitobello A, Chan MC, Fung JL, Rech M, Abicht A, Aubert Mucca M, *et al*: O'Donnell-Luria-Rodan syndrome: Description of a second multinational cohort and refinement of the phenotypic spectrum. J Med Genet, 2021 (Epub ahead of print). doi: 10.1136/jmedgenet-2020-107470.
3. Zhang X, Novera W, Zhang Y and Deng LW: MLL5 (KMT2E): Structure, function, and clinical relevance. Cell Mol Life Sci 74: 2333-2344, 2017.
4. O'Donnell-Luria AH, Pais LS, Faundes V, Wood JC, Sveden A, Luria V, Abou Jamra R, Accogli A, Amburgey K, Anderlid BM, *et al*: Heterozygous variants in KMT2E cause a spectrum of neurodevelopmental disorders and epilepsy. Am J Hum Genet 104: 1210-1222, 2019.
5. Shen E, Shulha H, Weng Z and Akbarian S: Regulation of histone H3K4 methylation in brain development and disease. Philos Trans R Soc Lond B Biol Sci 369: 20130514, 2014.
6. Li Y, Fan L, Luo R, Yang Z, Yuan M, Zhang J and Gan J: Case Report: De novo variants of KMT2E cause O'Donnell-Luria-Rodan syndrome: Additional cases and literature review. Front Pediatr 9: 641841, 2021.
7. Dong S, Walker MF, Carriero NJ, DiCola M, Willsey AJ, Ye AY, Waqar Z, Gonzalez LE, Overton JD, Frahm S, *et al*: De novo insertions and deletions of predominantly paternal origin are associated with autism spectrum disorder. Cell Rep 9: 16-23, 2014.
8. Schell R, Martin N Mullis, Takeshi Matsui, Ryan Foree and IM Ehrenreich: Genetic basis of a spontaneous mutation's expressivity. BioRxiv, 2020. doi:10.1101/2020.04.03.024547.
9. Cooper DN, Krawczak M, Polychronakos C, Tyler-Smith C and Kehrer-Sawatzki H: Where genotype is not predictive of phenotype: Towards an understanding of the molecular basis of reduced penetrance in human inherited disease. Hum Genet 132: 1077-1130, 2013.
10. Shulha HP, Cheung I, Whittle C, Wang J, Virgil D, Lin CL, Guo Y, Lessard A, Akbarian S and Weng Z: Epigenetic signatures of autism: TrimethylatedH3K4landscapes in prefrontal neurons. Arch Gen Psychiatry 69: 314-324, 2012.
11. Zech M, Boesch S, Maier EM, Borggraefe I, Vill K, Laccone F, Pilshofer V, Ceballos-Baumann A, Alhaddad B, Berutti R, *et al*: Haploinsufficiency ofKMT2B, encoding the lysine-specific histone methyltransferase 2B, results in early-onset generalized dystonia. Am J Hum Genet 99: 1377-1387, 2016.
12. Sharawat IK, Panda PK and Dawman L: Clinical characteristics and genotype-phenotype correlation in children with KMT2E gene-related neurodevelopmental disorders: Report of two new cases and review of published literature. Neuropediatrics 52: 98-104, 2021.
13. Conforti R, Iovine S, Santangelo G, Capasso R, Cirillo M, Fratta M and Caranci F: ODLURO syndrome: Personal experience and review of the literature. Radiol Med 126: 316-322, 2021.
14. Bosemani T, Orman G, Boltshauser E, Tekes A, Huisman TA and Poretti A: Congenital abnormalities of the posterior fossa. Radiographics 35: 200-220, 2015.