Molecular Genetics and Metabolism Reports 33 (2022) 100927

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Case Report

A novel *de novo* pathogenic variant in *KDM3B* gene at the first Albanian case of Diets-Jongmans syndrome: DIJOS

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ARTICLE INFO

Keywords:
KDM3B gene
Impaired intellectual development
Short stature
Facial dysmorphism

ABSTRACT

Diets-Jongmans syndrome, DIJOS, is a very recently described autosomal dominant condition, which is caused by heterozygous pathogenic variants in *KDM3B* gene and characterized by impaired intellectual development, short stature, as well as facial dysmorphism. We describe a new DIJOS patient harboring a heterozygous, novel, *de novo* and likely pathogenic variant in *KDM3B* gene, which is the first case reported after Diets et al.`s publication, to the best of our knowledge.

1. Introduction

Diets-Jongmans syndrome (DIJOS) is an autosomal dominant condition described for the first time by Diets et al., 2019 [1]. Pathogenic variants in *KDM3B* gene (lysine-specific demethylase 3B [MIM: 609373; GenBank: NM_016604.3]) on chromosome 5q31 are responsible for Diets-Jongmans syndrome [1]. The gene is involved in histone H3-K9 demethylation and thought to control transcription through RNA polymerase II. [1,2]. Diets et al. have found that all the patients they studied showed developmental delay (DD) or mild to moderate intellectual disability (ID), and that the majority of them had behavioral issues, as well as feeding difficulties in childhood. These patients also have a distinct facial appearance with a large mouth, pointed chin, long ears, low columella and short stature (described as short stature below 2.5SD) [1]. We are describing a case, of a new pediatric patient with a novel, heterozygous pathogenic variant in *KDM3B* gene as well as his clinical and facial characteristics.

2. Case report and discussion

Our early childhood patient, presents delayed motor and speech development, short stature and facial dysmorphism. He manifests autistic features with language deficits and lack of spoken language but uses some gestures to interact and has eye communication. His vocabulary consists of less than 10 words with many phonetic difficulties. Parents even define him as “extremely lazy” to play and talk. Delayed echolalia, stereotypic repetitive movements of the hand fingers (especially when he is excited) are present. When called by name, most of the time he turns his head, uses pointing and can interact with key figures and close family members. He creates games with them but with lot of encouragement and help. He had delayed motor milestones and still has difficulties with fine motor skills. He had feeding difficulties, had started solid food at the age of five months with a lot of feeding difficulties with vomiting or spitting and till the age of seven months he did not accept any food other than breast milk which led to significant weight loss. He has short stature with height/age at −2,5 SD and slightly underweight with weight/age at −1,07 SD. Long ears, a prominent nasal tip, a thin upper lip and a broad mouth with a severe dental caries were some of his facial features which also drew our attention (Fig. 1).

Because clinical genetic sequencing is widely used to diagnose individuals with unexplained neurodevelopmental problems, we performed the genetic testing [3]. Genomic DNA was extracted from peripheral blood in dried blood spot and the genetic test was developed and its performance was validated by CENTOGENE Gmbh (whole exome sequencing based on TWIST capture probes and Illumina short-read sequencing technology) [4]. Molecular genetic testing in our patient identified a heterozygous likely pathogenic variant in *KDM3B* gene [c.305_315delinsTATGCT p.(Glu102Valfs*25)] which creates a shift in the reading frame starting at codon 102. The new reading frame ends in a stop codon 24 positions downstream.

Abbreviations: DIJOS, Diets-Jongmans syndrome.

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https://doi.org/10.1016/j.ymgmr.2022.100927
Received 25 August 2022; Received in revised form 11 October 2022; Accepted 12 October 2022

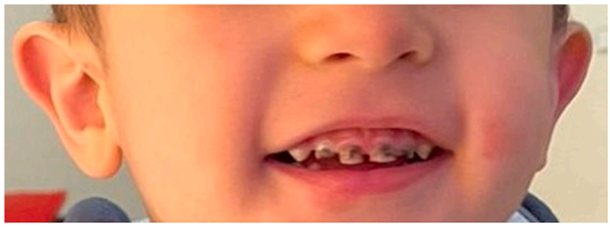

Fig. 1. Facial characteristics of patient: long ears, a prominent nasal tip, a thin upper lip, a broad mouth, severe dental caries.

Diets et al. discovered pathogenic heterozygous missense and truncating germline variants in *KDM3B* gene of all patients using exome sequencing, demonstrating that both *de novo* and inherited variants in *KDM3B* gene cause DIJOS syndrome and indicating that KDM3B haploinsufficiency seems to be probably the cause of this condition [1].

The identified variant in our case was not found neither in his parents nor in any of Diets' patient groups, indicating that it is a novel and *de novo* pathogenic variant in *KDM3B* gene [1]. It was also not detect any class 1 or 2 variants in the genes, for which secondary (incidental) findings are reported.

The clinical characteristics of our patient are similar with those of previously reported by Diets's group [1]. They found a number of clinical features in common in their patients, such as delayed motor and speech social-emotional development, aggressive behavior, ADHD and autism, hyperactivity but not formal psychiatric diagnoses, epilepsy, childhood hypotonia, microcephaly, a distinct facial appearance, short stature, eye abnormalities, hearing loss, joint hypermobility, wide range of congenital anomalies and hematological malignancies [1].

Although most of these clinical characteristics are currently present in our patient, we would like to point out that we will continuously follow him, so as to monitor their evolution and observe, hence making sure whether any additional clinical features, which might broaden the phenotypic spectrum of DIJOS, will occur. The mutational and clinical characteristics of DIJOS are very well characterized in our patient confirming this diagnosis in our case as described, which would be, to the best of our knowledge, the first case reported after the publication of Diets et al.

This case also highlights the fact how sequencing technology has aided in finding a rising number of neurodevelopmental disorders (NDDs)-related genes [1,3,5]. Finding disease-related genes can help in early diagnosis, for the genotype phenotype correlation and a better understanding of the disease's pathogenesis, as well as enable patients to access the best possible care [3,5].

Contributors

MT, PC conceived the structure and content, wrote and revised the manuscript. ST made essential contribution to the manuscript. ST, ED performed the clinical evaluation of the patient. OP and PB were involved on genetic data analysis, interpretation and editing of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding

This case study received no external funding. All the tests were free of charges.

Ethical compliance

The study was performed in accordance with the ethical standards of the national ethics committee and received their approval. Patient consent for publication: Obtained.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

The data that has been used is confidential.

Acknowledgement

The authors thank and acknowledge the patient and his family. Also, the authors would like to acknowledge the Albanian Society of Rare Diseases.

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