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CASE REPORT

Novel genetic variant causing Arboleda-Tham syndrome

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Abstract

We report the case of a 10-year-old boy followed since birth due to a polymalformative syndrome, including congenital cardiac disease, microcephaly, failure to thrive, trunk hypotonia and hypertonia of the extremities. With time, chief complaints were developmental delay and absence of expressive language. On physical examination dysmorphic facial features became more evident. The chromosomal analysis and array comparative genomic hybridization (aCGH) revealed no significant pathogenic changes. Whole Exome Sequencing (WES) identified the likely pathogenic variant c.4027dup p.(Glu1343Glyfs*13) in heterozygosity in KAT6A gene. This variant results in the production of a truncated protein and was not reported previously in the literature. Pathogenic variants in the KAT6A gene cause Arboleda-Tham Syndrome (ARTHS), which has variable clinical presentations. This boy´s features and severe developmental defects are compatible with the ones described in other cases of late-truncating pathogenic variants in this gene. Reviewing the literature, we found out that this is the first patient in Portugal diagnosed by WES and that it involves a novel reported genetic variant.

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INTRODUCTION

In 2015, heterozygous pathogenic variants in the *KAT6A* gene (OMIM 601408), on chromosome 8p11, were discovered as causing a mental retardation and developmental delay syndrome later referred to as the KAT6A or Arboleda-Tham syndrome (ARTHS) (OMIM #616268)[1]. Since then, around 80 cases have been described in the literature delineating a new syndrome with variable presentation, that depends upon de location of the pathogenic variant in the *KAT6A* gene[2].

The core features of this syndrome are intellectual disability (ID), speech delay, with receptive language consistently more developed than expressive language, microcephaly, cardiac anomalies, and gastrointestinal complications with high incidence of gastroesophageal reflux and constipation. It is also associated with some variable dysmorphic facial features, poor overall growth and hypotonia, some with stiff extremities, and visual defects, including strabismus[3,4].

KAT6A gene (also known as *MYST3*, *MOZ*) consists of 17 exons and encodes a lysine acetyltransferase[5]. If the pathogenic variant is proximal, the transcript undergoes nonsense mediated decay, and symptoms arise through haploinsufficiency. Transcripts with pathogenic variants in exons 16 and 17, however, may not be degraded, and consequently encode a truncated protein that acts in a dominant-negative or gain-of-function manner[1,5]. Truncating *KAT6A* pathogenic variants in the last exon or close to the last exon resulted in more severe phenotypes than truncating variants in earlier exons[1]. Over 50 protein-truncating, six missense and four splicing variants have been identified across the whole *KAT6A* gene. Patients with missense variants have not, to date, shown a cardiac phenotype[6].

The wide phenotypic spectrum in individuals with *KAT6A* variants highlights the continued importance of exome sequencing to identify the genetic etiology for patients with syndromic ID[7].

CASE REPORT

We report the case of a male child, currently with 10 years old, followed in consultation since he was a newborn for polymalformative syndrome.

Gypsy ethnicity, with consanguineous parents (second cousins) and consanguineous maternal grandparents. The father has a cognitive delay with absent language, epilepsy and strabismus and the mother was positive for HCV infection. Healthy paternal brothers.

Uneventful antenatal history, except for the mother that is positive for HCV infection; normal ultrasounds and fetal echocardiography. Birth at 37 weeks of gestation with apgar scores 8/10. At physical examination he presented congenital microcephaly (percentile <5), weight and length at percentile 10 and a systolic breath. A transfontanellar ultrasound was performed with normal results and echocardiography detected a large subaortic ventricular septal defect, pulmonary valve stenosis and patent foramen ovale with left-to-right shunt. Cardiac defects required corrective surgery at 13 months old.

In the first months of life, he maintained a poor height-weight evolution, had progressive microcephaly, with greater distance from the 5th percentile and presented axial hypotonia with peripheral spasticity. He had recurrent respiratory infections and a history of constipation. At 3 months old he presented a convulsive crisis, with hospitalisation.

Of the study carried out during hospitalization and thereafter he presented alterations in the electroencephalogram with generalised and scarce paroxistic activity, and a remaining normal study, which included: HCV PCR; metabolic study; mitochondrial respiratory chain complexes and histological examination of muscle biopsy; karyotype 46,XY; study by multiplex ligation-dependent probe amplification (MLPA) of syndromes associated with mental retardation (Kit P064: 1p36, 5q35.3/Sotos, 7p/Saethre-Chotzen, 7q11.23/williams, 15q11.2/Prader-Wili, 17p13.3/Miller-Dieker, 17p11.2/Smith-Magenis, 20p12.2/Alagille, 22q11.2/DiGeorge); deletion search on chromosome 22, region 22q11.2, utilizing Fluorescence In Situ Hybridization (FISH); Array comparative genomic hybridization (aCGH). Brain magnetic resonance imaging at 11 months and repeated at 8 years old showed Chiari malformation type 1 and microcephaly.

The patient maintained follow up in multidisciplinary consultations, namely paediatric cardiology, metabolic disorders, and neuropediatry. Evaluation by paediatric ophthalmology and otorhinolaryngology was normal.

Over the years delayed psychomotor development become more evident, with absent expressive language. He had no other convulsive crisis. Some features of the objective examination have become more pronounced such as a dysmorphic face with bitemporal narrowing, prominent nasal bridge, thin upper lip and downturned corners of the mouth (figures 1 and 2).

At 9 years old, Whole Exome Sequencing (WES) detected the likely pathogenic variant c.4027dup p.(Glu1343Glyfs*13) in *KAT6A* gene (NM_006766.4), in the heterozygous state. This is a frameshift variant located at exon 17, that introduces a premature stop codon, expected to result in the production of a truncated protein. This variant was not previously reported in the literature and is not present in the population database, the genome aggregation Database (gnomAD). It was, therefore, classified as a likely pathogenic variant according to the American College of Medical Genetics and Genomics (ACMG) guidelines[8]. Pathogenic variants in the *KAT6A* gene cause ARTHS.

Currently with 10 years old, the patient integrates a multideficiency unity with speech and occupational therapies. He presents a very scarce language and absence of sphincter continence, with frequent need of laxatives due to constipation.

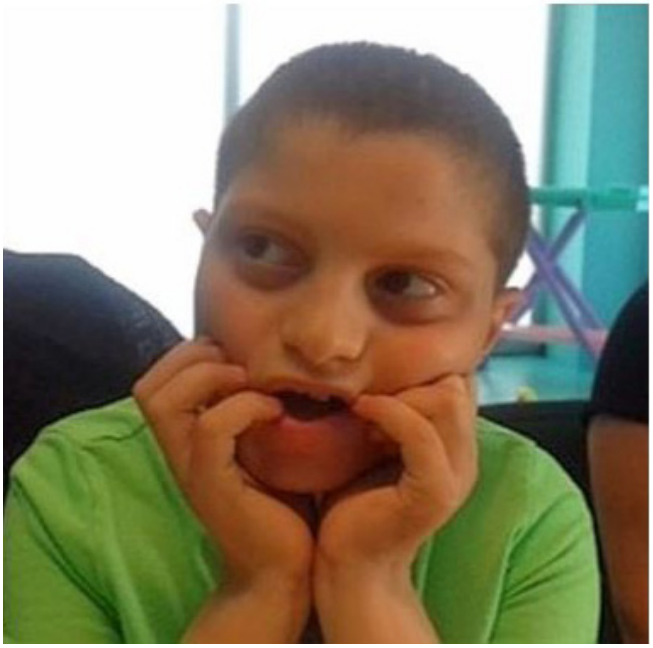


Figure 1. Dysmorphic facial features with bitemporal narrowing, prominent nasal bridge, thin upper lip and downturned corners of the mouth.

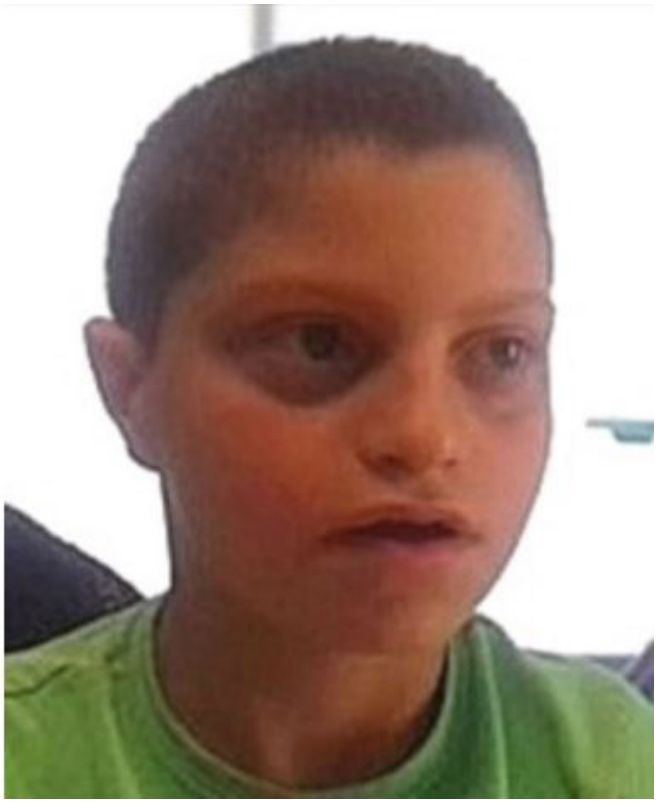


Figure 2. Dysmorphic facial features with bitemporal narrowing, prominent nasal bridge, thin upper lip and downturned corners of the mouth.

DISCUSSION

To our best knowledge, this is the first Portuguese ARTHS patient detected by WES and he has a novel variant.

Over the past few years the number of newly identified pathogenic variants in *KAT6A* has been increasing, expanding the genotypic and phenotypic spectrum of this syndrome[1].

The likely pathogenic variant identified in our patient is a late-truncating mutation, located in exon 17. Severe development delay with almost absent language, microcephaly and dysmorphic facial features were observed. The severe phenotype presented by the patients, with development delay, almost absent language, microcephaly and dysmorphic facial features, is in accordance with previous reports which have shown that clinical presentation is more severe in late-truncating pathogenic variants[3].

According to the core features usually present in ARTHS, Kennedy et al. (2019)[7] recommended that all patients with *KAT6A* pathogenic variants have an electrocardiogram and an echocardiogram. They also recommended early speech and language therapy, close follow-up by gastroenterology, and regular ophthalmologic evaluation, which corresponds with part of the follow-up of our patient even prior to the diagnosis.

The study of the parents is recommended to determine whether the detected variant is inherited or "de novo" and this result must be communicated in the context of genetic consultation. In the presented case, the study of the patient´s progenitors is currently underway. *KAT6A* pathogenic variants known to date are inherited in a dominant manner and, in general, arise *de novo.* However, a few inherited *KAT6A* pathogenic variants were reported in a cohort of 76 patients, some of which were inherited from mosaic parents[1,7].

In conclusion as the genetic databases become more complete, the use of WES in diagnosis patients with syndromic development delay will be more powerful[3].

LEARNING POINTS

- The wide phenotypic spectrum in individuals with *KAT6A* variants highlights the continued importance of exome sequencing (WES) to identify the genetic etiology for patients with syndromic intellectual disability
- We report the first Portuguese with Arboleda-Tham syndrome patient detected by WES and he has a novel variant.
- As the genetic databases become more complete, the use of WES in diagnosis patients with syndromic development delay will be more powerful

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