Identification of an emerging heterozygous variant in KAT6A by whole exome sequencing: a case report

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Background: Arboleda-Tham syndrome is an autosomal dominant disorder caused by mutations in the lysine acetyltransferase 6A (*KAT6A*) gene, leading to intellectual disability and a broad phenotypic spectrum. Diagnosis can be challenging due to phenotypic heterogeneity. The aim of this study was to define the genetic basis of unexplained global developmental delay in a Chinese boy and expand the *KAT6A* mutational spectrum.

Case Description: We report a 4-year and 7-month-old Chinese boy who presented with global developmental delay, severe intellectual disability, and markedly limited expressive language. Physical examination revealed no seizures, cardiac malformations, or growth retardation. Initial chromosomal copy number variation sequencing (CNV-seq) detected no pathogenic abnormalities. To identify the underlying molecular defect, whole-exome sequencing (WES) was performed on the proband and both parents. WES revealed a novel, *de novo* heterozygous frameshift variant (c.4099del, p.Glu1367Argfs*40) in exon 17 of the *KAT6A* gene. Sanger sequencing confirmed the absence of this variant in either parent, supporting its *de novo* origin. The mutation is predicted to introduce a premature termination codon 40 amino acids downstream and is classified as pathogenic according to American College of Medical Genetics and Genomics (ACMG) criteria.

Conclusions: This report expands the mutational spectrum of *KAT6A* and underscores the critical diagnostic utility of WES in children with unexplained neurodevelopmental disorders, enabling precise genetic counseling and avoiding unnecessary investigations.

Keywords: Lysine acetyltransferase 6A (*KAT6A*); whole exome sequencing (WES); gene variants; mental retardation; case report

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Introduction

Lysine acetyltransferase 6A (*KAT6A*; also known as monocytic leukemia zinc finger protein) has been implicated in various neoplasms and biological processes, including leukemia (1), leukemic cell proliferation, and breast cancer (2). In patients with Arboleda-Tham syndrome, variants in the *KAT6A* gene frequently lead to either loss of function or abnormal function of the KAT6A protein,

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impacting various biological processes, particularly those related to neurodevelopment. The core features of the syndromes associated with *KAT6A* variants include mental retardation (3), delayed language development (where receptive language skills consistently exceed expressive language skills), microcephaly (4), cardiac malformations (5), and gastrointestinal complications. It is also associated with a variety of different facial malformations, poor overall growth, hypotonia, stiff limbs, and vision problems in some patients. It is evident that multiple phenotypes manifest among patients with the same syndrome, including varying degrees of developmental delay, a range of dysmorphic features, and other complications. The specific location and nature of the *KAT6A* variant play a significant role in determining the clinical presentation. However, the intricate molecular mechanisms underlying the development of this disease remain under investigation, and, regrettably, there is currently no effective treatment for Arboleda-Tham syndrome. This case report details a Chinese boy with a late truncating variant in the *KAT6A* gene. It provides insights into the diagnosis of *KAT6A* syndrome, and in the absence of definitive treatment guidelines, the patient has received speech and motor training. We present this case in accordance with the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-2025-aw-695/rc).

Highlight box

Key findings

- A novel *de novo* heterozygous frameshift variant (c.4099del, p.Glu1367Argfs*40) was identified in the lysine acetyltransferase 6A (*KAT6A*) gene of a pediatric patient diagnosed with Arboleda-Tham syndrome. The patient exhibited core neurodevelopmental features of the syndrome, including severe intellectual disability, global developmental delay, and profound expressive language impairment. This variant is located within the C-terminal acidic-rich domain (exon 17), a recognized mutational hotspot, and is predicted to result in a loss-of-function through protein truncation.

What is known and what is new?

- Pathogenic variants in the lysine acetyltransferase gene *KAT6A* are the established cause of Arboleda-Tham syndrome, characterized by a variable phenotype of intellectual disability, speech delay, and potential multi-systemic involvement.
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What is the implication, and what should change now?

- This case underscores the diagnostic efficacy of whole exome sequencing (WES) in children experiencing unexplained global developmental delay or intellectual disability, particularly when first-tier tests such as chromosomal microarray yield negative results. Clinicians should consider the early implementation of WES in the diagnostic journey of these patients to facilitate precise molecular diagnoses, guide management strategies, and provide accurate genetic counseling regarding recurrence risks. Future research should concentrate on the functional validation of specific truncating variants, such as c.4099del, and on elucidating the mechanisms that connect C-terminal *KAT6A* dysfunction to the observed neurodevelopmental phenotype.

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of Jinan Children's Hospital (Children's Hospital Affiliated to Shandong University) (No. SDFE-IRB/T-2025161). Written informed consent was obtained from the patient's parent for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Clinical presentation and history

The child is a 4-year and 7-month-old boy male who presents with developmental delays, specifically mental retardation, and limited active language skills. At the age of 3 years, he was able to call out "mom" and "dad", but his language development has been slow; currently, he can only produce 1–2 words and understands approximately 10 words. He responds to his name and follows some commands but is unable to point to identify the five senses or distinguish colors. Socially, he can engage in play with other children, primarily through chasing games, although he participates in very few interactive games and often engages in babbling. There are no evident stereotypical behaviors or special interests noted. The child demonstrates good physical abilities, such as running quickly and jumping on both feet, and he maintains a healthy appetite and sleep pattern. He exhibits no urinary or fecal abnormalities and has no significant medical history. His gross motor development appears consistent with that of typically developing peers. He has an older brother in the second grade with normal intelligence. His parents are healthy with

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normal intelligence and neurodevelopment. Upon physical examination, the child was alert and exhibited a clear mental state, with no skull deformities or distinctive facial features. His respiration was stable, breath sounds were clear bilaterally, and heart sounds were strong and rhythmic.

Genetic investigations: methodology and findings

Genetic testing revealed a negative copy number variation sequencing (CNV-seq) result. To establish a molecular diagnosis, whole exome sequencing (WES) was employed. Genomic DNA (gDNA) was extracted from the peripheral blood samples of the proband using the QIAamp DNA Blood Midi Kit (QIAGEN, Hilden, Germany), following the manufacturer's instructions. A total of 500 ng of gDNA was captured utilizing the FreySeq® Whole Exome Library Preparation and Hybridization Capture Kit (V2.0 plus+mt) (Fujungenetics Biotechnology Co., Ltd., Shanghai, China). The captured libraries were sequenced on the Illumina NovaSeq 6000 platform (Illumina, Inc., San Diego, CA, USA) with 150 bp paired-end reads. Raw sequencing data underwent quality filtering to produce clean reads, which were subsequently aligned to the human reference genome (GRCh37/hg19) using the Sentieon software package. More than 99% of the target regions were covered, with an average sequencing depth exceeding 150×. Duplicate reads were identified and removed using Picard, and variant calling for single nucleotide variants (SNVs) and small insertions/deletions (indels) was conducted using the Genome Analysis Toolkit (GATK). The detected variants were annotated and filtered against several population databases, including the National Center for Biotechnology Information (NCBI) Single Nucleotide Polymorphism database (dbSNP), HapMap, the 1000 Genomes Project, and the Exome Aggregation Consortium (ExAC). Pathogenic variants were screened via the Human Gene Mutation Database (HGMD) and ClinVar. The pathogenicity of the remaining variants was assessed according to the guidelines established by the American College of Medical Genetics and Genomics (ACMG). Functional predictions were executed using the Alamut® Software Suite (Interactive Biosoftware, Rouen, France) and Ensembl. Copy number variations (CNVs) were analyzed using an in-house exon-based detection tool (CNVexon), while pseudogene optimization was conducted using a published misalignment detection algorithm (6).

WES identified a *de novo* heterozygous variant c.4099del p.Glu1367Arg fs*40 in the *KAT6A* gene (located on chromosome 8 at position 41792327). This variant involves the deletion of a base at position 4099 in the coding sequence, leading to the substitution of glutamic acid (Glu) at position 1367 with arginine (Arg) and resulting in a frameshift variant that introduces a premature termination codon after the 40th predicted amino acid following the frameshift. To confirm the identified variant and assess its inheritance pattern, Sanger sequencing was performed on gDNA obtained from the proband and both parents. Primers were specifically designed to flank the target region, and sequencing was conducted following standard protocols. Chromatograms were meticulously analyzed to verify the presence or absence of the variant. The sequencing results from both parents showed no abnormal variants in the targeted region, indicating that the mutation was not inherited from either parent. The Sanger sequencing results further confirmed the presence of this variant, as evidenced by overlapping peaks observed at approximately 510–520 bases. Additionally, the signal intensity and peak shape observed at approximately 520–530 bases exhibited anomalies consistent with the shifted variant (*Figure 1*). This variant was absent from the gnomAD v4.1.0 population database, supporting its rarity and potential pathogenicity.

Discussion

KAT6A is a member of the MYST family of proteins and forms a histone acetyltransferase (HAT) complex, which plays a crucial role in regulating transcriptional activity and gene expression (7). *KAT6A* variants were first identified by Arboleda *et al.* (4) and Tham *et al.* (3). In 2015, *KAT6A* variants have been identified in this disorder as missense, splice, and protein truncation variants. The number of patients with pathogenic *KAT6A* variants has rapidly increased in recent years, with over 100 cases reported to date, thereby contributing to the definition of the broad phenotypic spectrum of the syndrome (8). The *KAT6A* gene consists of 17 exons that encode a protein comprising 2004 amino acids. *KAT6A* contains several key functional domains, each serving a distinct role (9): the nuclear localization signal (NLS), a specific amino acid sequence that facilitates the localization of the protein to the nucleus, typically located at or near the N-terminus of *KAT6A*; and two plant homeodomain (PHD) (PHD 1 and PHD 2), which assist in the protein's nuclear localization by binding to acetylated amino acids. The structural domains of KAT6A proteins facilitate the recognition and binding to chromatin through their interaction with the acetylated histone3

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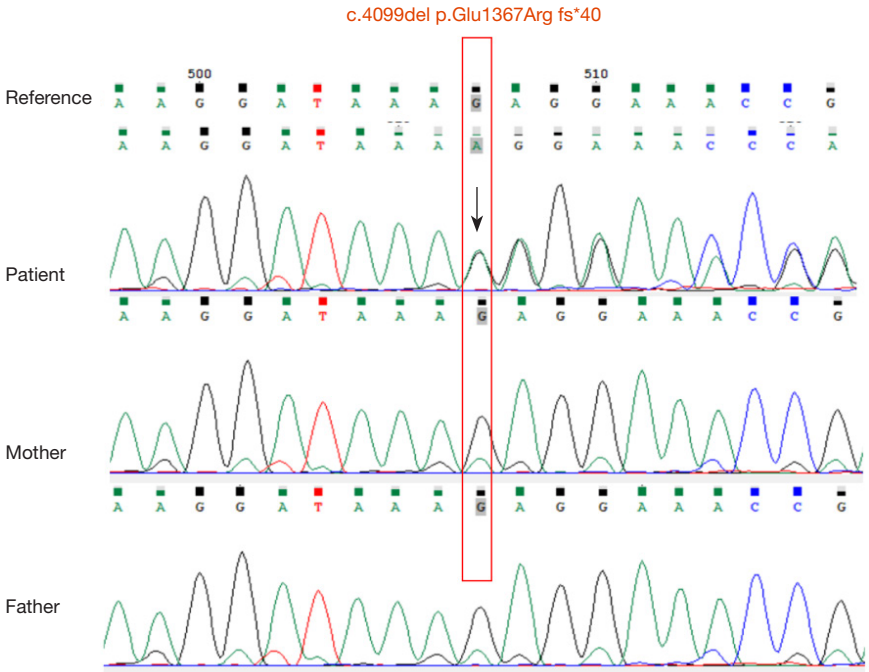


Figure 1 Sanger sequencing verified the variant of KAT6A gene c.4099del P.Lu1367ARG fs*40. Direct comparison of the called DNA sequences for the proband and his parents against the reference sequence is shown. The numerical labels (500, 510) denote the approximate starting base-pair positions within the sequencing read. The heterozygous c.4099del frameshift variant is present in the proband's sequence (arrow), resulting in p.Glu1367Arg fs*40. The corresponding chromatogram profiles for each sample—displaying overlapping peaks at the variant site (~510–520 bp) in the proband and wild-type traces in both parents—are provided in the original electrophoretic data files (Figures S1-S3). Translation of the mutant allele [Lys-Asp-Lys-Gly-Lys-Pro … (fs*40)] confirms the altered reading frame initiated by the deletion. The absence of the variant in both parental sequences confirms its *de novo* origin.

N-terminal tail, thereby regulating gene transcription. The HAT structural domain, a core functional region of *KAT6A*, is responsible for the acetylation of histones, a process that modifies the chemical structure of histones and relaxes chromatin, making genes more accessible for transcription. Additionally, the acidic glutamate/aspartate-rich region, which is abundant in glutamate and aspartic acid, enhances the binding of proteins to one another and may play a synergistic role in chromatin remodeling, gene transcription, and other biological processes. The serine- and methionine-rich region, which is similarly enriched in these amino acids, is crucial for protein phosphorylation and methylation modifications, both of which are integral to signaling and the dynamic regulation of proteins, ultimately influencing the activity, stability, and interactions of the KAT6A protein with other proteins (10).

Furthermore, the trans-activation domain is a significant functional domain within *KAT6A*, typically associated with transcription factor activity, and is essential for initiating gene expression, regulating chromatin structure, and shaping gene expression profiles. Most *KAT6A* variants are concentrated in exons 16 and 17 within the glutamate/aspartate-rich structural domain (8). For instance, the c.4099 del variant of the *KAT6A* gene is in exon 17, resulting in a variant that truncates the protein at the 40th amino acid. This truncating variant may lead to the loss of HAT function of *KAT6A*, consequently disrupting the associated transcriptional regulation processes.

The clinical manifestations of patients with *KAT6A* gene variants primarily include developmental delay and varying degrees of intellectual disability, along with speech delays and disorders affecting both speech and movement. A significant number of patients also present with congenital heart disease (11), characterized by cardiac malformations such as atrial septal defects, ventricular septal defects, and persistence of fetal anatomical structures; notably, a considerable percentage of these patients require surgical intervention. In the gastrointestinal system, symptoms may

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include intestinal obstruction, vomiting, dry heaving, anal stenosis, and gastroesophageal neurological dysfunction. Recent reports have also noted fetal hepatic calcification in some patients (12). Hematologically, a few cases of aplastic anemia (13) and hereditary globoid erythrocytosis (14) have been documented. Additionally, a small subset of patients exhibits premature closure of cranial sutures (15,16), microcephaly (17), frequent infections, ocular strabismus (18), congenital hearing defects, epilepsy (19), feeding difficulties, and oral motor dysfunction. The location and type of *KAT6A* variants significantly influence clinical outcomes; early truncating variants are typically found in exons 1–15, while late truncating variants are located in exons 16–17. Clinical studies indicate that late truncating variants are associated with more severe manifestations, suggesting that early and late truncating variants may reflect different genetic mechanisms (20). Our patient's variant, situated in exon 17, is classified as a late truncating variant. Given that severe speech delay and intellectual disability are prevalent features among patients with *KAT6A* variants, the specific variant observed in our patient does not present a distinctive phenotype but aligns with the expected clinical presentation.

Diagnosing the disease based solely on phenotype is challenging. This case clearly demonstrates that WES serves as an effective diagnostic tool. We recommend the timely scheduling of WES to facilitate early diagnosis and personalized treatment for patients with similar presentations. The number of patients with pathogenic *KAT6A* variants has steadily increased since the initial discovery of the *KAT6A* gene variant. Our report contributes to this growing body of evidence by presenting a case associated with a novel, potentially pathogenic *KAT6A* variant.

The underlying molecular mechanisms of mental retardation caused by *KAT6A* variants remain largely unknown. Recent studies have demonstrated that *KAT6A* deficiency disrupts synaptic structure and plasticity in the hippocampal Cornu Ammonis 3 (CA3) region. Moreover, R-spondin 2 (Rspo2), a gene enriched in CA3 that encodes the Wingless/Integrated (Wnt) activator Rspo2, has been identified as a key transcriptional target of *KAT6A*. Deletion of Rspo2 in excitatory neurons has been shown to impair memory formation, while restoration of Rspo2 expression in CA3 neurons can rescue deficits in Wnt signaling and learning-related behaviors in *KAT6A* mutant mice. Thus, this pathway is crucial for regulating synaptic plasticity and cognitive function in the hippocampal CA3 region (21). The discovery of this pathway may also provide a potential therapeutic target for syndromes associated with *KAT6A* gene variants.

Conclusions

In conclusion, we present a case of a *de novo* heterozygous variant in *KAT6A* in our patient, whose clinical presentation closely resembles that of individuals previously reported with Arboleda-Tham syndrome. We propose that early WES may facilitate diagnosis, potentially enabling the patient to avoid unnecessary testing and to receive timely interventions. At present, there are no established guidelines for the diagnosis and treatment of this condition, highlighting the need for further functional studies of this variant to identify therapeutic targets for future management.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-2025-aw-695/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-2025-aw-695/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki and its subsequent amendments. The study was approved by the

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Ethics Committee of Jinan Children's Hospital (Children's Hospital Affiliated to Shandong University) (No. SDFE-IRB/T-2025161). Written informed consent was obtained from the patient's parent for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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