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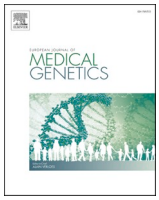

Clinical Report

Fetal hepatic calcification in severe KAT6A (Arboleda-Tham) syndrome

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ABSTRACT

Arboleda-Tham syndrome (ARTHS, MIM 616268) is a rare genetic disease, due to a pathogenic variant of Lysine (K) Acetyltransferase 6A (*KAT6A*) with autosomal dominant inheritance. Firstly described in 2015, ARTHS is one of the more common causes of undiagnosed syndromic intellectual disability. Due to extreme phenotypic variability, ARTHS clinical diagnosis is challenging, mostly at early stage of the disease. Moreover, because of the wide and unspecific spectrum of ARTHS, identification of the syndrome during prenatal life rarely occurs. Therefore, reported cases of *KAT6A* syndrome have been identified primarily through clinical or research exome sequencing in a gene-centric approach.

In order to expands the genotypic and phenotypic spectrum of ARTHS, we describe prenatal and postnatal findings in a patient with a novel frameshift *KAT6A* pathogenic variant, displaying a severe phenotype with previously unreported clinical features.

1. Introduction

Arboleda-Tham syndrome (ARTHS, MIM 616268) is a rare genetic disease, due to a pathogenic variant of Lysine (K) Acetyltransferase 6A (*KAT6A*) with autosomal dominant inheritance. Firstly characterized in 2015, ARTHS is one of the more common causes of undiagnosed syndromic intellectual disability. KAT6A belongs to the MYST family of proteins (KAT6A, KAT6B, KAT5 and KAT7) that are involved in a wide range of fundamental cellular functions, such as chromatin remodeling, gene regulation, protein translation, and cell replication (Bae et al., 2021). KAT6A is the enzymatic core of a histone-acetylation protein complex, and, highly expressed in early development, it plays a key role in cell-type specific differentiation (Bae et al., 2021; Rokudai et al., 2013; Alkhateeb and Alazaizeh, 2019; Borrow et al., 1996; Tham et al., 2015; Wang et al., 2022).

ARTHS clinical spectrum is wide and often unspecific, including global developmental delay, primary microcephaly, and craniofacial dysmorphism, as well as more varied features such as feeding difficulties, cardiac defects, and ocular anomalies. Currently, due to restricted knowledge and phenotypic variability, ARTHS clinical diagnosis is challenging, mostly at early stage of the disease. Moreover, because of the wide and unspecific spectrum of ARTHS, identification of the syndrome during prenatal life rarely occurs. Indeed, reported cases of *KAT6A* syndrome have been identified primarily through clinical or research exome sequencing (ES) in a gene-centric approach (Kennedy et al., 2019).

In order to expands the genotypic and phenotypic spectrum of ARTHS, we describe prenatal and postnatal findings in a patient with a novel frameshift *KAT6A* pathogenic variant, displaying a severe phenotype with previously unreported clinical features. Furthermore, this case emphasizes the timely conduction of genetic analysis for the early diagnosis to spare patients from meaningless examinations and ineffective treatments.

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2. Clinical report

The proband was the second daughter, born from healthy non-consanguineous Albanian parents. During the first trimester of gestation, the combined screening test resulted at high risk for trisomy 21 (MoM of PAPP-A 0.29), while the cell free DNA was at low risk. Amniocentesis was performed at 16 weeks of gestation and karyotype was 46, XX normal. At 31 gestational weeks, the prenatal ultrasound showed dolichocephaly, deviated heart axis, dilated right cardiac section, high cardio-thoracic ratio and liver calcifications (Fig. 1). The infant was delivered at 38 weeks of gestation by cesarean section due to breech presentation. Apgar scores were 6 and 7 at 1st and 5th minutes, respectively. Birth weight was 2890 g (27th centile, SDS -0,62), length was 47 cm (15th centile, SDS -1,04), and head circumference was 34 cm (57th centile, SDS 0,17) (Bertino et al., 2012).

The infant presented neonatal respiratory distress and needed non-invasive ventilatory support (CPAP) for 24 hours. Since first days of life, dysmorphic features were evident: large forehead, sparse eyebrows, prominent nasal bridge, thin upper lip, low-set ears with cupped left ear, micrognathia, wide thumb and wide first toe bilaterally, 5th finger of feet overlapping to the other fingers. Cardiac ultrasound showed ostium secundum atrial septal defect (ASD) and muscular ventricular septal defect (VSD). Abdomen ultrasound confirmed liver calcifications, predominant in the 7th segment. Congenital infections (TORCH and parvovirus) were ruled out. Auditory brainstem response test (ABR), ophthalmic examinations, cranial ultrasound resulted normal. Postnatal karyotype was 46, XX normal. CGH-array showed a non-pathogenic 102 kb microdeletion of chromosome 2, del2q13(110862477_110964737), inherited from the father. At 10 months of age, brain and spine magnetic resonance (MRI) (Fig. 2), showed dolicocephalic skull, supratentorial ventriculomegaly and tonsillar descent (Arnold Chiari type 1 malformation), arachnoid cysts in the ponto-cerebellar cisternae, agenesis of the 12th thoracic vertebra, fibrolipoma in the distal portion of the filum terminale. Due to ventriculomegaly, she underwent a third ventricle-cisterno-stomy at the age of 11 months.

Since the first months of life severe global developmental delay was evident (Table 1). In the first two years of life, she suffered of frequent upper respiratory tract infections, requiring hospitalization, and she presented feeding difficulties. She also developed obstructive sleep apneas (OSAS), needing nocturnal CPAP ventilation. Electroencephalogram did not show epileptic anomalies. At the last follow up visit, 24 months of age, auxological data were: 9300 g weight (4th centile, SDS -1,81), 84 cm length (22nd centile, SDS -0.77) and 41.5 cm head circumference (0^{th} centile, SDS -4,11). The child presented microcephaly, severe psychomotor delay, absent language, deficient sitting position, limb hypertonia, poor motor coordination, and she received a variety of rehabilitation therapies (Supplemental figure).

Next generation sequencing (NGS) panel, including 150 genes causing intellectual disability (ID) showed a novel de novo heterozygous c.3721delG, p.(Glu1241Lysfs*53) frameshift variant in the exon 17 of the *KAT6A* gene (NM_006766.5); this variant is likely pathogenic according to 2015 American College of Medical Genetics and Genomics guidelines (Richards et al., 2015). The c.3721delG *KAT6A* gene variant was submitted to ClinVar (SCV004171188).

3. Discussion

ARTHS is a recently described monogenic disorder, characterized by extreme phenotypic variability. Within last years, the number of patients identified with pathogenic *KAT6A* variants has rapidly expanded and, up to now, more than 100 cases have been reported, contributing to define the broad phenotypic spectrum of the syndrome. ARTHS is characterized by mild to severe ID, developmental and speech delays, hypotonia and congenital heart defects, along with less penetrant features such as seizures, microcephaly and autism spectrum disorder (Tham et al., 2015; Kennedy et al., 2019; Arboleda et al., 2015). We summarize the *KAT6A* related clinical manifestations, as described in the literature in Table 2.

Herein, we have reported on a patient with a novel de novo heterozygous *KAT6A* frameshift variant, presenting previously unreported

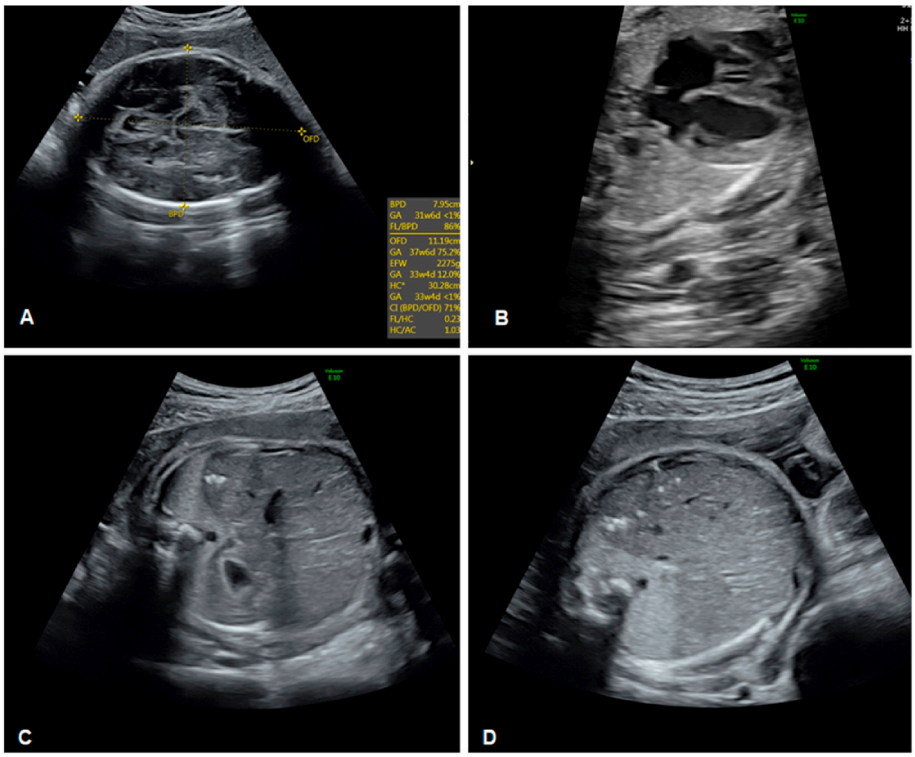

Fig. 1. Prenatal ultrasound performed at 31 weeks of gestation showed an abnormal cranial shape with dolichocephaly (A), abnormal cardiac axis (B) and liver calcifications (C–D).

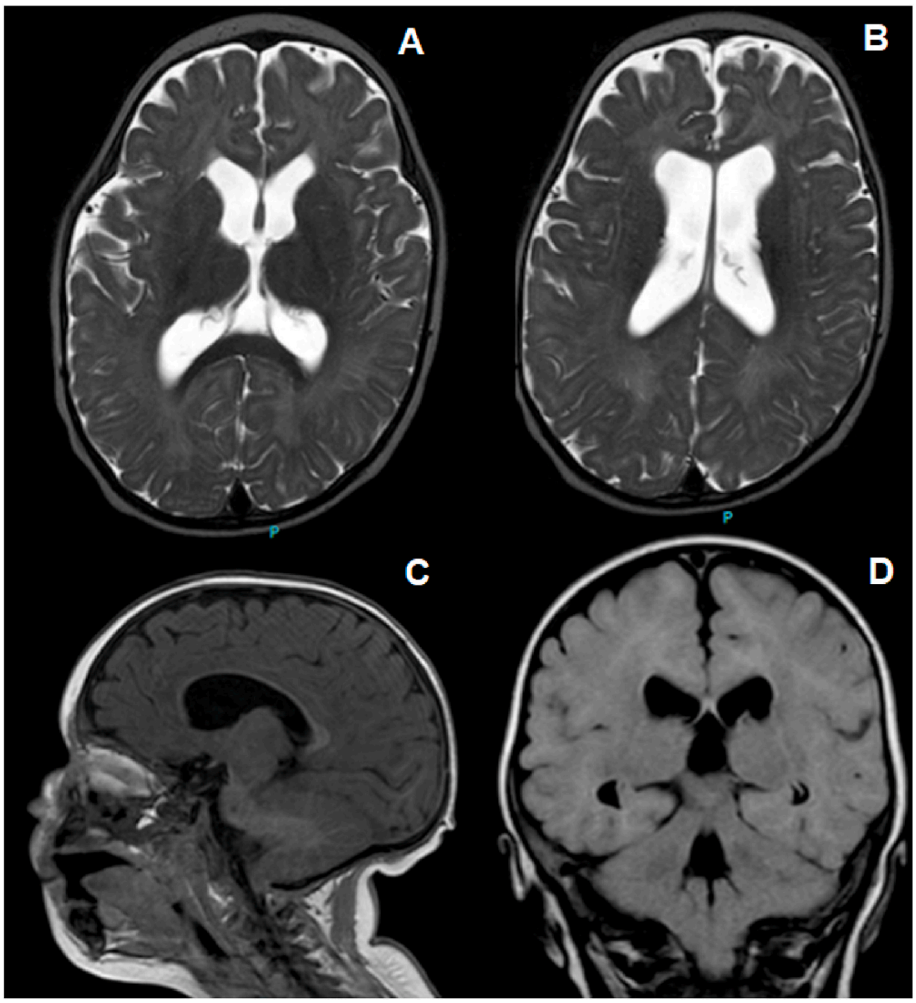

Fig. 2. Cerebral MRI performed at 10 months of age.1A and 1B: axial T2 weighed images, showing supratentorial ventriculomegaly and reduced white matter. 1C: sagittal T1 weighted images showing thin corpus callosum and tonsillar descent. 1D: 3D HR MRI displaying small posterior cranial fossa with partially narrowed forth ventricle, wedge-like and descended cerebellar tonsils (Arnold Chiari type 1 malformation).

features and severe phenotype. Indeed, since the prenatal period our case showed several peculiar abnormalities (dolicocephaly, enlarged right cardiac section, liver calcification), which, although non-specific, could lead to suspicion of a genetically determined condition. Fetal liver calcification, occasionally noted at autopsy or ultrasound, are relatively common, but their biological importance is still incompletely explored. Previous reports highlighted an association to infection, circulatory compromise, malformations or chromosomal abnormalities. Identification of a fetal calcification together with a malformation doubles the probability of detecting a chromosomal abnormality, compared with a malformation alone (Sahlin et al., 2015). Therefore, ultrasound detection of fetal calcification should infer special attention towards co-existence of malformations, as this would be a strong indicator for a chromosomal abnormality. On the contrary, in cases of isolated and stable fetal liver calcification, after ruling out infectious diseases and chromosomal abnormalities, the prognosis is generally considered favorable (Simchen et al., 2002). Anyway, although fetal karyotyping is recommended in fetal calcification (mostly when additional structural anomalies are present), the association of fetal liver calcification with monogenic syndromic conditions (and not even with ARTH) has never been reported. With regard to antenatal diagnosis, because of the wide and unspecific spectrum of ARTHS presentation, diagnosis of the syndrome during prenatal life is only reported in two fetuses with congenital heart disease and investigated with ES (Agarwal et al., 2023). Although ES is not routinely used in prenatal clinical diagnosis, the association of liver calcifications and cardiac abnormalities may lead to consider whether performing ES or genetic panel including *KAT6A* gene, in addition to traditional fetal chromosomal microarray analysis and karyotype. As ID is the most prominent clinical feature of ARTHS, prenatal diagnosis may benefit families to consider termination of pregnancy due to the increased risk of severe neurological compromise.

Because of the broad phenotypic spectrum, it is difficult to diagnose ARTHS based on clinical symptoms alone, even during postnatal life. In this regard, the recent study by Bukvic adopted the “Phenomizer”, to avoid clinical bias and to perform searches based on sets of precise phenotypic abnormalities. “Phenomizer” is a web-based application for clinical diagnostics in human genetics, using semantic similarity searches in the human phenotype ontology. Bukvic et al. highlighted the most frequent signs and symptoms of ARTHS, in order to address the diagnostic suspicion and convey the subsequent genetic investigations (Bukvic et al., 2023).

In addition to previously reported ARTHS features, our patient displayed also peculiar spine abnormalities, like agenesis of the 12th thoracic vertebra and fibrolipoma of the filum terminale. However, due to the relatively small number of patients reported in literature, novel phenotypic findings must be cautiously taken into consideration, given that they might not be directly related to the ARTHS. Nevertheless, our patient exhibited an extremely severe phenotype with significant neurological impairment and no developmental milestones

Table 1
Case report's clinical characteristics.

AGE	At birth	At discharge *(13 days of life)*	3 months of life	18 months of life	24 months of life
WEIGHT	2890 g (27 centile, SDS -0,62)^	2905 g (6°, SDS – 1,58)*	5800 g (27°, SDS – 0,60)*	9300 g (24°, SDS – 0,70)*	9300 g (4°, SDS – 1,81)*
LENGHT	47 cm (15 centile, SDS – 1,04)^	49 cm (11°, SDS – 1,22)*	61 cm (44°, SDS – 0,16)*	78 cm (22°, SDS – 0,76)*	84 cm (22°, SDS – 0,77)*
HEAD CIRCUMFERENCE	34 cm (57 centile, SDS 0,17)^	33 cm (4°, SDS – 1,73)*	37 cm (<1°, SDS – 2,60)*	41.5 cm (<1, SDS – 3,37)*	41.5 cm (<1°, SDS – 4,11)*
DEVELOPMENTAL DELAY	Poor and feeble cry	Limb and girdle hypertonus.	Hypotonia, abnormal general movements (absent fidgety), poor motor activity and absent interaction.	Sitting position not achieved. Girdle hypertonus.	Sitting position not achieved. Limb hypertonus, poor motor coordination.Severe psychomotor delay with absent language.
FACIAL FEATURES	Large forehead, sparse eyebrows, prominent nasal bridge, thin upper lip, low-set ears with cupped left ear, micrognathia	Large forehead, prominent nasal bridge, thin-tented upper lip, low-set ears with cupped left ear,	Prominent nasal bridge, thin-tented upper lip, low-set ears with cupped left ear, large forehead, Sparse eyebrows and micrognathia	Prominent nasal bridge, thin-tented upper lip, low-set ears with cupped left ear, large forehead, Sparse eyebrows and micrognathia	Prominent nasal bridge, thin-tented upper lip, low-set ears with cupped left ear, large forehead, Sparse eyebrows and micrognathia
CARDIAC MALFORMATIONS	ND	Ostium secundum atrial septal defect (ASD) and muscular ventricular septal defect (VSD)	Ostium secundum atrial septal defect (ASD)	ASD	ASD
ORO-INTESTINAL PROBLEMS	Poor sucking, orogastric tube feeding	Sucking and swallowing were poorly coordinated	Feeding difficulties	Rehabilitation for pharyngo-esophageal incoordination	Persistent feeding difficulties.
SKULL AND BRAIN ABNORMALITIES	Microcephaly	Normal cranial ultrasonography, unless hyperechogenic thalamo-striatal striae bilaterally	Microcephaly	Cerebral MRI performed after third ventricle-cisterno-stomy shower reduced lateral ventricles, thin corpus callosum, reduced sub-cortical white matter, small posterior fossa with tonsillar descent in the setting of Arnold-Chiari I malformation, small arachnoid cysts in the ponto-cerebellar cisternae	ND
OTHER CLINICAL FEATURES	ND	Hyperechogenic spots in the right lobe of the liver with predominant localization to 7th segment	ND	T12 agenesis and fibrolipoma of the filum terminale	ND

achievement. Although ID, microcephaly and hypotonia are common in ARTHS, such a severe phenotype with global impairment is rarely described. Interestingly, our patient showed a novel de novo heterozygous c.3721delG, p.(Glu1241Lysfs*53) frameshift variant in the exon 17 of the *KAT6A* gene.

The *KAT6A* gene comprises 18 exons (16 coding), encoding a protein 2004 amino acids in size. *KAT6A* contains several important functional domains: a nuclear localization domain (including H15), a double-plant homeodomain finger that binds to acetylated histone H3 tails (PHD 1 and 2), a histone-acetyl-transferase domain (HAT), an acidic glutamate/aspartate-rich region, and a serine and methionine-rich region that comprises a transactivation domain 4–7 (Tham et al., 2015). Most of the pathogenic mutations characterized to date are protein-truncating mutations that occur throughout the length of the gene, but most commonly in the two last exons that accounts for more than half of the gene. Missense mutations to the enzymatic histone-acetyltransferase domain or highly conserved C-terminus regions have also been associated with ARTHS, however, the phenotype is less-severe than the protein-truncating mutations (Kennedy et al., 2019). Moreover, in the study of Kennedy et al., a correlation between the site of the mutation and the level of ID, was observed: 95% of late truncating cases (exon 16 and 17) were rated as moderate-to-severe ID, while 60% of early truncating cases (exons 1–15) were rated as mild (Kennedy et al., 2019). Specifically, they observed a greater severity of ID and a higher frequency of microcephaly, hypotonia, cardiac abnormalities, and gastrointestinal complications associated with truncating mutations in the last two exons. This suggests a potential role for nonsense mediated decay (NMD), where truncating mutations in the first 15 exons trigger NMD mechanisms and result in haploinsufficiency; by contrast, mutations in exons 16 and 17 would not cause NMD, therefore the mRNA would be translated in a dysfunctional protein that may have gain-of function or dominant negative effects (Kennedy et al., 2019; Urreizti et al., 2020; Wright et al., 2015; Zeng et al., 2022). The novel de novo heterozygous c.3721delG, p.(Glu1241Lysfs*53) *KAT6A* variant of our patient is located in the acidic domain, which is rich in arginine residues, and it is considered a "hot spot" domain. Like the majority of reported pathogenic variants (occurring in the ultimate and penultimate exons of the gene), this frameshift variant is located in the last exon (Kennedy et al., 2019; Zou et al., 2021; Gauthier-Vasserot et al., 2017).

Our patient presented most of the ARTHS features, including global developmental delay, microcephaly, feeding difficulties, congenital heart defects, and frequent infections. In addition, she displayed less frequently reported features, like OSAS and Arnold Chiari I malformation with secondary hydrocephalus, and unreported abnormalities, like liver calcification, vertebral malformations and fibrolipoma of the filum terminale. Nevertheless, our data fit with the previously reported trend, (Kennedy et al., 2019) in which there is more severe global developmental delay and ID in patients with pathogenic variants located in exon 16 or 17, but the most notable aspect of this case is the exceptionally severe phenotype, which occurs in a patient with a frameshift *KAT6A* variant, rather than a truncating one.

4. Conclusion

Our report contributes to expand the genotypic and phenotypic spectrum of ARTHS, describing a new case with a novel frameshift

Table 2
Arboleda-Tham syndrome's clinical manifestations.

Intellectual disability (ID), abnormalities of the skull and brain	▪ ID mild to severe (Kennedy et al., 2019) ▪Developmental delay (Kennedy et al., 2019) ▪Marked expressive speech delay (as a form of verbal dyspraxia) (Kennedy et al., 2019) with more developed receptive language (Kennedy et al., 2019) ▪Hypotonia (contributes to motor delay) (Bae et al., 2021) ▪Limb hypertonia (more notable in the neonatal period) (Bae et al., 2021) ▪Microcephaly (in 41.0% of patients; less common in early-truncating variants) (Bae et al., 2021) Brain malformations include: (Kennedy et al., 2019) ▪pituitary malformation ▪thin corpus callosum ▪delayed myelination ▪large cisterna magna ▪variant venous anatomy (abnormal venous sinus crossing the falx cerebri) ▪Hydrocephalus ▪Arnold-Chiari malformation Epilepsy is reported in ~20% of patients: (Troisi et al., 2022) ▪infantile spasms responsive to anti-seizures medications ▪focal seizures ▪absences
Cardiac malformations	In 51% of Kennedy et al.'s cohort: (Kennedy et al., 2019) ▪atrial septal defects (34%) ▪ventricular septal defects (8%) ▪persistence of the fetal anatomy (19%): patent foramen ovale, persistent ductus arteriosus
Gastrointestinal problems	78% of patients experienced feeding difficulties (commonly associated with verbal dyspraxia due to oro-motor dysfunction). (Kennedy et al., 2019) ▪many patients required nasogastric feeding at birth, others had a gastrostomy tube for feeding, a small number underwent fundoplication ▪dysphagia ▪significant gastro-esophageal reflux ▪food allergy (Richards et al., 2015) Less frequent gastrointestinal problems in early-truncating variant (Urreizti et al., 2020)
Facial features	Most frequent facial features (Kennedy et al., 2019; Urreizti et al., 2020) ▪broad/bulbous nasal tip (in 86% of patients, which may become more obvious with age) ▪thin, tented upper lip ▪frontal bossing ▪bi-temporal narrowing ▪prominence of the nasal bridge ▪short and flat philtrum Less frequent (Kennedy et al., 2019; Urreizti et al., 2020) ▪epicanthic folds ▪low set and posteriorly rotated ears, occasionally folded ▪high arched narrow palate ▪teeth abnormalities (abnormal peg-shaped teeth, small tooth size, supernumerary teeth and dental crowding)
Eye features	▪strabismus (in 54% of patients) (Kennedy et al., 2019) ▪refractive errors: myopia is more commonly than hypermetropia (Kennedy et al., 2019) ▪delayed visual maturation, cortical visual impairment and astigmatism (Kennedy et al., 2019) ▪photophobia, latent horizontal nystagmus and Jeavons epilepsy (in an isolated cases) (Kennedy et al., 2019)
Behavioral problems	▪Anger outbursts, inappropriate laughter, hand-waving, increased anxiety (Kennedy et al., 2019) ▪Autism and autistic features (reported in ~25% of newly cases of KAT6A syndrome) (Munuera-Cabeza et al., 2022)
Hematological and Immunological Associations	▪Frequent infections ▪B-cell and T-cell immunodeficiency ▪Hypogammaglobulinemia ▪Unexplained persistent thrombocytopenia (Kennedy et al., 2019)
Sleep disorders	▪Difficulty in initiating and maintaining sleep (recurrent restless sleep) ▪Central obstructive sleep apnea (Kennedy et al., 2019) ▪Snoring (Smith and Harris, 2021)
Other clinical features	▪Undescended testicles (males) ▪Clinodactyly ▪Brachydactyly (Kennedy et al., 2019) ▪Skeletal abnormalities (scoliosis, torticollis, and kyphosis) founded in 29 patients (Munuera-Cabeza et al., 2022)

KAT6A pathogenic variant and unreported clinical features, beginning from prenatal life. The knowledge of ARTHS variegated phenotypic spectrum may help clinicians to a timelier diagnosis, improving clinical management and sparing patients from un-necessary diagnostic examinations.

Statement of conflicts of interest

Each author declares that he or she has no commercial associations that might pose a conflict of interest in connection with the submitted article.

Patient recruitment

The patient's parents provided written informed consent to perform genetic testing and to publish clinical pictures together with the full content of this publication in accordance with the Declaration of Helsinki (1984) and its subsequent revisions, same as for any other applicable local ethical and legal requirements.

CRediT authorship contribution statement

Antonella Di Caprio: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Cecilia Rossi:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization. **Emma Bertucci:** Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Luca Bedetti:** Supervision, Validation, Visualization, Writing – review & editing. **Natascia Bertoncelli:** Supervision, Validation, Visualization. **Francesca Miselli:** Supervision, Validation, Visualization, Writing – review & editing. **Lucia Corso:** Supervision, Validation, Visualization. **Carolina Bondi:** Supervision, Validation, Visualization. **Lorenzo Iughetti:** Supervision, Validation, Visualization, Writing – review & editing. **Alberto Berardi:** Supervision, Validation, Visualization, Writing – review & editing. **Licia Lugli:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2023.104906.

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