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Clinical Report

Phenotypic variability in a family with an inherited *KAT6A* frameshift variant

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ABSTRACT

KAT6A syndrome or Arboleda-Tham Syndrome (ARTHS; OMIM #616268) is a syndromic neurodevelopmental disorder mainly presenting with variable degrees of intellectual disability (ID) and developmental delay (DD), especially speech delay, hypotonia and autism spectrum disorders/behavioral problems. Multiple organ-systems including eyes, heart, gastrointestinal and neurological system can be involved. Other phenotypic features with a suggested association to *KAT6A* include immune dysfunction and pituitary anomalies. Initially, ID/DD was reported as universal in KAT6A syndrome; however, two children with normal assessment of intellect and development at age 10 and 11 years, were recently reported. KAT6A syndrome is caused by heterozygous pathogenic variants in *KAT6A*. Inherited variants are rare, and to our knowledge, only three inherited missense variants in *KAT6A* have been reported, whereas frameshift and nonsense variants have been inherited from mosaic parents only.

Here, we report a Danish family, where an inherited *KAT6A* frameshift variant c.2710dup (p.(Glu904Glyfs*12)) show clinical variability in disease phenotype expression among three family members. The description includes an affected first child with premature pubarche (the first individual to our knowledge), a mildly affected second child with normal cognitive performance assessment (the third reported individual with normal assessment of cognition and KAT6A syndrome), and a self-sufficient adult family member. The description expands the phenotypic spectrum of KAT6A syndrome, and thus brings important knowledge for improved management and counselling of patients and families with this rare condition.

1. Introduction

Arboleda-Tham Syndrome (ARTHS; OMIM #616268) or KAT6A syndrome is a syndromic neurodevelopmental disorder mainly presenting with variable degrees of intellectual disability (ID) and developmental delay (DD) (93–100%), especially speech delay (99–100%), hypotonia (76%) and autism spectrum disorders/behavioral problems (23–45%). Multiple organ-systems can be involved, including impaired vision and/or eye anomalies (77%), structural cardiac anomalies (44%), gastrointestinal concerns (69%), movement disorder (47%), microcephaly (31%) and seizures (22%) (Kennedy et al., 2019; Arboleda et al., 2015; Tham et al., 2015; Urreizti et al., 2020; St John et al., 2022). Other phenotypic features with a suggested association to *KAT6A* include immune dysfunction (Kennedy et al., 2019; Newman et al., 2016) and pituitary anomalies (Zwaveling-Soonawala et al., 2017).

Initially, ID/DD was reported as universal in KAT6A syndrome (Kennedy et al., 2019; Urreizti et al., 2020). However, a recent report of 49 individuals identified two children with normal assessment of intellect and development at age 10 and 11 years, respectively (St John et al., 2022). Also, 13 out of the 49 individuals were classified as verbal, though with varying language delay in childhood (St John et al., 2022).

The KAT6A foundation has identified approximately 350 individuals diagnosed with KAT6A syndrome (KAT6A.org), and more than 80 individuals have been published (Kennedy et al., 2019; Urreizti et al., 2020; St John et al., 2022). Most publications concern children, though adults are present, including a case of late onset epilepsy (Kennedy et al., 2019; St John et al., 2022; Trinh et al., 2018). However, knowledge of neurocognitive prognosis and late onset symptoms is still sparse.

KAT6A syndrome is caused by heterozygous pathogenic variants in *KAT6A* that encodes Lysine acetyltransferase 6 A (also called MYST3 or

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MOZ) (Arboleda et al., 2015; Tham et al., 2015). As a member of the MYST family, MYST3 is an epigenetic modulator of chromatin structure and gene transcription that functions via acetylation of histones (Voss et al., 2009; Wiesel-Motiuk and Assaraf, 2020). MYST is also involved in acetylation of non-histone proteins such as the tumor suppressor p53, a key factor in cell cycle arrest and apoptosis (Rokudai et al., 2013). The majority of reported *KAT6A* variants have occurred *de novo* (Kennedy et al., 2019). In 2018, the first case of an inherited variant was published, and the authors suggested that familial cases are primarily caused by missense variants causing milder phenotypes (Trinh et al., 2018). To our knowledge, only two other cases of inherited missense variants as well as one case with a frameshift variant found in a mosaic state in maternal blood (Kennedy et al., 2019) and one case of suspected germline mosaicism in a parent of three children with the same nonsense variant, have been published (Kennedy et al., 2019; Satoh et al., 2017). Considering protein truncating variants, a genotype-phenotype correlation has been reported: increased severity of ID was more common in patients having late truncating variants (last two exons 16 and 17) compared to patients having early truncating variants (exon 1–15) (Kennedy et al., 2019; St John et al., 2022).

We report a previously unreported inherited *KAT6A* frameshift variant, c.2710dup (p.(Glu904Glyfs*12)), and describe the corresponding phenotype in three individuals in a Danish family: An affected first child with premature pubarche (the first individual to our knowledge), a mildly affected second child with normal cognitive performance assessment (the third reported individual with normal assessment of cognition and KAT6A syndrome), and a self-sufficient adult father. Their phenotypes are compared to previosly reported phenotypic findings in KAT6A syndrome (Table 1).

2. Clinical report

2.1. Patient 1

Patient 1 is a now 9 years and four-month-old girl, the first child of healthy, non-consanguineous parents. Routine ultrasound (US) in the first and the second trimester revealed no abnormalities. At gestational age (GA) 31 + 5 (weeks + days), US performed due to transient bleeding from the vagina revealed fetal growth restriction (−21,7 %) and a slightly reduced flow in the middle cerebral arteria. Fetal cardiotocography (CTG) was normal. Subsequent US showed persistent fetal growth restriction, but normal flow in the middle cerebral artery. The girl was delivered by Cesarean section at GA 35 + 6 due to brain sparing, and severely reduced fetal movements, reduced flow in the middle cerebral artery, abnormal fetal CTG as well as persistent fetal in utero growth restriction (IUGR). Pathological examination of the placenta revealed focal inflammation and ischemic changes with small infarctions. Maternal workup for thrombophilia was normal. Birth weight was 2140g (−1.5 SD), length 44 cm (−1.6 SD), head circumference 34 cm (+1.5 SD). Apgar scores were full, however, due to low birth weight and prematurity there was a one week need for hospitalization. Early motor development was normal: sitting independently at 8 months, standing independently at one year, and walking at one year; cognitive development was not described.

At four months of age, a systolic murmur was noted, and echocardiography showed a minor ventricular septal defect (VSD) and patent ductus arteriosus (PDA). Transcatheter PDA closure was performed at 9 months of age. Subsequent echocardiography showed a minor patent foramen ovale.

In early childhood, the girl had frequent admissions to hospital due to upper respiratory tract infections and asthmatic bronchitis, and later frequent episodes of otitis media required tubulation.

At three years of age, she did not pass hearing test (Automatic transient evoked otoacoustic emissions: A-TEOAE), and hearing aid was installed, though removed one year later due to normal hearing and no signs of auditive neuropathy.

Speech and development were assessed at three years of age, as her only spoken words were *yes* and *no* at that time. An almost complete lack of expressive speech (ROWPVT-test), with challenged oromotor skills was observed. Receptive speech delay, though milder, was observed as well (NRDLS-test). Cognitive assessment (SON-R test) showed mild to moderate intellectual disability, with particular challenges in executive functions. Social skills were unremarkable, and gross motor-skills were normal to slightly delayed (Baley, movement-ABC). At five years and 6 months, an increase in receptive language was observed, while expressive speech was still with monosyllable words exclusively. Cerebral magnetic resonance imaging (MRI) showed no structural anomalies, but a secondary finding of a supra-cellular arachnoid cyst measuring 4,6 cm was reported; this cyst was later removed by endoscopy. The patient suffered from frequent and worsening headaches, and sleep disturbance with difficulties falling asleep and wakening two to three times a night, though responding to melatonin. Additional cerebral MRIs were performed with normal results, and with sufficient flow through the fenestrated cyst; an eye examination was without signs of increased

Table 1
Phenotypic findings in the three patients reported. Y: Yes/affected, (Y): Finding suspected but not formally assessed, N: No/Not affected, NI: No information/Not investigated, (N): Finding not suspected but not formally assessed.

Findings	Patient 1	Patient 2	Patient 3	Frequency in individuals with ARTHS (Kennedy et al., 2019)
Sex	F	M	M	
Age: Years, months at latest follow up	9.4	7.0	36	
Motor delay	N	N	(N)	
Intellectual disability	Y (Mild to moderate)	N	(Y) (presumed mild)	100 %
Speech delay	Y	Y	(Y)	100 %
Neonatal hypotonia	N	N	NI	76 %
Impaired vision or eye anomaly	Y (left exotropia, astigmatism, hypermetropia)	NI	Y (Strabismus, glasses)	≥63 %
Constipation, reflux	N	N	(N)	≥60 %
Structural cardiac defects	Y (VSD, PDA)	N	N	51 %
Microcephaly	N	N	(N)	31 %
Seizures	N	N	N	9 %
Sleep disturbance	Y	N	N	37 %
Behavioral problems	N	N	N	39 %
Frequent infections	Y (upper respiratory tract infections in infancy)	N	Y (recurrent myocarditis in adulthood)	47 %
Facial Dysmorphology	Y	Y (mild)	Y	Common
Other	Supracellular arachnoid cyst, premature pubarche, frequent fractures	Postnatal poor growth, frequent fractures	N	

intracerebral pressure (ICP). As the headaches continued, ICP measurement was performed during 24 hours, showing episodes with slight pathological curves with ICP around 20 mmHg. Treatment with Diamox (Acetazolamide) was initiated.

Additionally, the patient had surgery for left exotropia at four years of age, mild vision impairment, astigmatism and hypermetropia (+2.25/+2.5).

At age 6 years and four months, the following findings were obtained: Height 118.4 cm (−0.5 SD), weight 27.1 kg (+1 SD), and head circumference 52.4 cm (0 SD). Facial dysmorphism comprising mild unilateral ptosis, short up-slanted palpebral fissures, hypertelorism, epicanthus, thin lips, and discrete hypermobility in elbows and knees were noted (See Fig. 1A).

At age 7 years and 10 months, the girl developed premature pubarche with pubic hair (Tanner scale: PH3), and breast development (B3). This could be secondary to increased ICP, or the fenestrated cyst in close relation to the pituitary gland. However, this was not confirmed by MRI of the brain. GnRH test was positive, and treatment was initiated to slow down puberty.

Of note, a total of three traumatic fractures occurred within the last two years: Spiral fracture of tibia after fall on bike, slow healing was noted; proximal fifth metatarsi avulsion after the foot got stuck in a door; and a Salter Harris type 1 epiphysiolysis of the lateral malleoli after fall on bike. Osteodensitometri, dual X-ray absorptiometry (DXA-scan) was normal, as well as bone markers in blood. The number of fractures was concluded to be within normal range for age, considering her level of activity and puberty growth spurt. At latest examination at age 8 years and one month, the following growth parameters where obtained: Weight: 33.9 kg (+1.5 SD), Height: 133.6 (+0.66 SD).

2.2. Patient 2

Patient 2 is a now 7-year-old boy, full sibling of Patient 1. The boy was delivered by elective Cesarean section at gestational age 33 weeks and 3 days due to slightly reduced growth in utero (−16%), brain sparing, and a history of IUGR in the sister (Patient 1), as well as a stillbirth of a second sister in week 37 (see note below, and Pedigree in Fig. 2). Until then, pregnancy had been uncomplicated, including 1. and 2. trimester routine US with no detected malformations. Birth weight was 2060 g (+0,3 SD), length 43 cm (−0,75 SD), head circumference 32,5 cm (+1,5 SD). Apgar scores were full, however, due to prematurity, neonatal hospitalization and early feeding were needed for 9 days. Early motor development was normal, and the first years were uneventful except for one episode of febrile convulsions. At age three years and one-month, speech and development were assessed (Bayley test), as his vocabulary consisted of 5–6 monosyllable words exclusively. Cognitive performance, motor skills, as well as receptive speech was normal for age. Expressive speech was un-assessable as the boy did not speak any words, but communicated with throat sounds only. An echocardiogram was performed, as well as hearing assessment (A-TEOAE), both with normal results. At that time, the boy was noted to have a poor growth at −2,5 to −2 SD when backtracking growth patterns. At age five years and

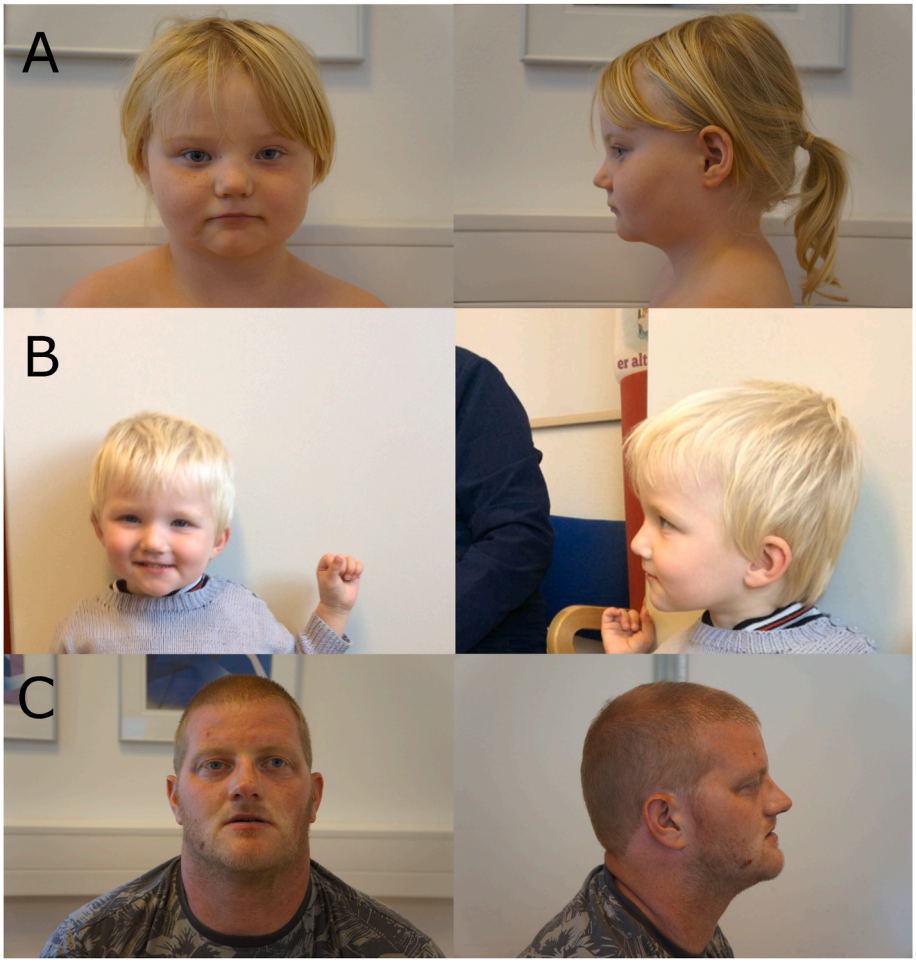

Fig. 1. A) Facial features of Patient 1 at six years: Mild unilateral ptosis, short and up-slanted palpebral fissures, hypertelorism and epicanthus, slightly prominent chin, thin upper and lower lips. B) Facial features of Patient 2 at three years: Mild epicanthus, prominent chin, thin upper and lower lips. C) Facial features of patient 3 at 34 years: Short and slightly up-slanted palpebral fissures, prominent chin, thin nose, thin upper and lower lip and short neck.

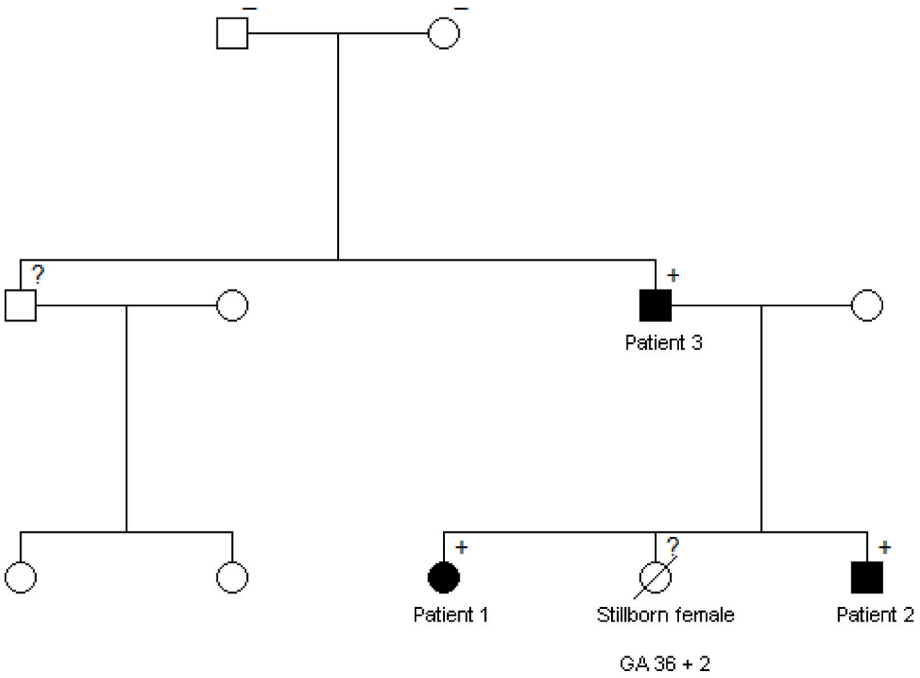

Fig. 2. Pedigree. +: *KAT6A* variant detected. -: *KAT6A* variant not detected. ? not tested
Square: male, circle: female. Crossed square/circle: deceased
Filled square/circle: phenotype consistent with KAT6A syndrome. Unfilled circle/square: No ID/DD or language developmental delay
Note: Regarding stillborn female GA 36 + 2: see clinical report, patient 2 for further information.

6 months, IGF-1 was assessed: 69,6 μg/l (−1,36 SD), but as growth was stable, no further evaluation was performed. The boy experienced 3 traumatic fractures within the last four years: a fifth finger fracture after getting pinched in the door, a greenstick fracture of the distal ulna following a fall from 1 m, and a dislocated supracondylar fracture of humerus following a jumping trauma. At the latest examination at age 7 years, he has a height of 112,8 cm (−2,5 SD). Radiographs of the hand show a bone maturation at 5,4 years (−1,16 SD). Cognitive assessment has not been formally re-evaluated, but noted as age appropriate regarding motor skills, as well as cognition, except for expressive language consisting of less than 30 words and with two-word sentences exclusively. Patient 2 has not been examined in our department, and information is obtained from his medical records after diagnosis, and facial dysmorphology from pictures (see Fig. 1B).

Note: Regarding a stillborn female sister (see Fig. 2 Pedigree). Routine US in the 1. trimester was normal. In GA 16 + 6, the pregnancy was complicated by maternal gallstones and pancreatitis. Routine US in GA 19 + 6 revealed no malformations. In GA 28 + 4, 31 + 4 and 33 + 4, US revealed persistent fetal growth restriction (−20%). In GA 36 + 2, IUGR persisted (−23%) and no fetal heart rate could be detected. She was delivered by Cesarean section. Autopsy of the still born girl revealed no apparent dysmorphology or malformations, asides from growth restriction. However, pathological examination of the placenta revealed a weight of 294 g (below 10th percentile) and accelerated maturation of the placental parenchyma. Maternal vascular malperfusion was the suspected cause of IUGR. Microarray of fetal tissue was performed, but leaving the case unresolved. Further genetic analysis was not wanted by the family.

2.3. Patient 3

Patient 3 is a now 36-year-old male, the father of Patient 1 and 2. He is the second child of healthy unrelated parents. Facial dysmorphic features consisting of short and slightly up-slanted palpebral fissures, thin lips, thin nose, slightly protruding chin and short neck (See Fig. 1C) were noted when the patient accompanied the daughter (Patient 1) at the clinical genetic department. The father had individualized education programs in elementary school and middle school. He was not able to graduate the ordinary middle school, as he did not complete the final exams, and he never went to high school. He initiated vocational training to become a mechanic, but dropped out. He now works full time in a subsidized employment as an unskilled carpenter due to problems with overview and planning of multiple working tasks, of which he is not able to accommodate more than maximum 1–4 tasks at a time. No formal cognitive testing has been conducted. Besides strabismus and the use of glasses, Patient 3 reported to be healthy in childhood. He reached an adult height of 184 cm (0 SD).

At 29 years of age, the patient was admitted to the hospital with fever up to 40.5 °C and stinging shoulder pain. Electrocardiography was normal except tachycardia with sinus arrests (up to 6 sec.). Chest X-ray, echocardiography and blood samples were also normal besides a slightly increased CRP (54 mg/l). Within days, the patient developed a mildly elevated procalcitonin. Cardiac MRI was normal. The episode spontaneously passed, and was concluded as possible myocarditis, based on blood samples and symptoms. However, one year later, the patient was admitted to the hospital with chest pain, responding to nitroglycerin. Preceding days with fever up to 40 °C and diarrhea. Blood samples showed elevated troponin I (171 ng/l), CRP (76 mg/l) and slight neutrophil leukocytosis (11x10^9/l). Electrocardiography was normal, but echocardiography showed reduced ejection fraction (EF) at 40–45%, and a discrete pericardial exudate. Again, myocarditis was the suspected diagnosis. Positive CMV- IgG and negative IgM were subsequently found. Over the subsequent years, additional two episodes of chest pain occurred with electrocardiography indicating atrial-ventricular block. Pace-maker implantation is considered.

3. Methods and results

Trio-based exome analysis on data from whole genome sequencing (WGS) was performed using DNA from blood from the girl (Patient 1) and both parents (as mentioned, father is Patient 3). DNA was prepared with Illumina DNA PCR Free library prep and sequenced using NovaSeq

6000 (Illumina) at a core facility in Aarhus University Hospital, Denmark. Average coverage was 30x. Initial data analysis followed a local NBA2 pipeline (Dept. of Molecular Medicine, Aarhus University Hospital) adhering to the GATK best practice recommendations. Further data analysis of the exome was performed using VarSeq version 2.2.4 (Golden Helix). Data was filtered for autosomal dominant *de novo* variants, autosomal dominant paternally inherited variants with association to relevant phenotype or with a CADD score >30, and autosomal recessive inherited variants (homozygous/compound heterozygous). Analysis of copy number variants (CNVs) was not performed. Reference genome: hg38.

Heterozygosity for a variant in *KAT6A* NM_006766.5:c.2710dup (p.(Glu904Glyfs*12)) was detected in the girl (Patient 1) and her father (Patient 3). This variant is not present in gnomAD v4.1.0 and is not previously reported (HGMD, 2024.2), but is predicted (Alamut Visual v.2.15.0) to change the reading frame and cause a premature stop codon. The variant was classified as likely pathogenic (PVS1, PM2) according to the ACMG classification guideline (Richards et al., 2015). WGS analysis identified no other relevant alterations. Subsequently, the same variant was identified in the boy (Patient 2). Segregation analysis identified that the variant was most likely *de novo* in the father, as it was not detected in any of his parents.

4. Discussion

Here, we present a previously unreported inherited *KAT6A* frameshift variant. As inherited variants in *KAT6A* are rare, description of the corresponding phenotype within a family with two affected siblings and their father adds important knowledge of intra-familial variability. The family demonstrates that the phenotypic spectrum of KAT6A syndrome within a family may be as broad as observed between families (inter-familial variability). The findings furthermore underline the importance of filtering for inherited variants, even in cases where the parents' phenotypes appear normal. As it is well documented that patients with a pathogenic *KAT6A* variants (subjects with confirmed KAT6A syndrome/ARTHS) have a particular DNA methylation signature, episignature is a useful diagnostic option for further confirmation of pathogenicity of the variant described in the patients/family; however, this was not possible as episignature is yet not accessible in our lab.

Language developmental delay is common in KAT6A syndrome, with expressive language often more severely affected than receptive language (Kennedy et al., 2019; St John et al., 2022). Verbal prognosis was addressed in a recent survey of detailed communication profiles in 49 individuals with KAT6A syndrome, as 13 of 49 individuals with varying language delay in childhood, were later classified as verbal (St John et al., 2022). In the family presented here, all three individuals had varying degrees of speech delays. The children (Patient 1 and 2) both had a profile of expressive language being more severely affected than receptive language, and both were classified as minimal-verbal (less than 30 words spoken). The father (Patient 3) was not formally assessed for language development, but speech delay in childhood was recalled. He is now fully verbal. Early truncating variants (defined as pathogenic variants in exon 1–15, as is the case for the variant presented here) tend to result in a milder phenotype (Kennedy et al., 2019; St John et al., 2022). However, ID/DD has been considered universal in KAT6A syndrome, and often in the severe range, but caution due to ascertainment bias has been emphasized (Kennedy et al., 2019; Urreizti et al., 2020). Recently, two individuals with normal assessment of intellect and development at ages 10 and 11 years, were reported (St John et al., 2022). In the family presented here, cognitive performance was normal in the brother (Patient 2), though he was still too young to undergo formal IQ testing. The sister (Patient 1) had mild to moderate intellectual disability. Cognition was not formally assessed in the father (Patient 3), and though he never completed final exams in the 9th grade, he is now working full time as an unskilled carpenter in a subsidized employment position. These emerging cases of normal cognition or very mild ID, as well as knowledge of the extend of verbal improvement, holds important information on the phenotypic spectrum, when counselling patients and families about KAT6A syndrome.

Growth patterns showed intrafamilial differences among individuals, as the brother had a continuous postnatal growth below his target (−2.5 to −2 SD), whereas the father (Patient 3) had a final height of 184 cm (0 SD), and the daughter (Patient 1), though small at birth, had normal growth parameters (+1.5 SD). Cardiac phenotypes differed as well: the girl (Patient 1) had a VSD and PDA, whereas the brother and father (Patient 2 and 3 respectively) had no cardiac structural anomalies.

Involvement of the immune system has been proposed in KAT6A syndrome (Kennedy et al., 2019; Newman et al., 2016). In this family, the girl (Patient 1) had frequent admissions to hospital in early childhood due to upper respiratory tract infections and frequent episodes of otitis media. However, she does no longer suffer from recurrent infections. The father (Patient 3) developed recurrent episodes of suspected myocarditis in adulthood. However, both findings are unspecific and neither were tested for immunodeficiency, and it remains uncertain if the findings are related to *KAT6A*.

Interestingly, the girl (Patient 1) presented with premature pubarche in addition to the common KAT6A syndrome manifestations. She is the first patient presenting with this symptom. Previously, a girl with KAT6A syndrome and multiple pituitary hormone deficiencies due to pituitary anomalies has been reported (Zwaveling-Soonawala et al., 2017). However, in the patient reported here, no pituitary anomalies were detected, and the finding could be secondary to a previously removed arachnoid cyst, or simply co-occurrence by coincidence. Both children (Patient 1 and 2) had frequent fractures, though normal bone markers in blood. It is uncertain if this feature is related to KAT6A syndrome.

In conclusion, we report a previously unreported inherited *KAT6A* variant and the corresponding phenotype in three family members. A detailed clinical description conveys the notably mild phenotype in one of the children and the children's father, and thus expands the phenotypic spectrum of KAT6A syndrome; this knowledge enables improved management and counselling of patients and families with this rare condition.

CRediT authorship contribution statement

Sidsel Bjerg Ringsted: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Sara Markholt:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Lotte Andreasen:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Pernille Axél Gregersen:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Consent

The patients (parents in case of minors) gave written informed consent to publication. Informed consent was also obtained prior to procedures involving patient data, and is in agreement with ethical standards of Aarhus University Hospital.

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Disclosure of conflict of interest

None.

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Data availability

The identified variant in *KAT6A* have been submitted in a publicly accessible database: Patient 1 (Decipher ID 540239).

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