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BRIEF COMMUNICATION

A *KAT6A* variant in a family with autosomal dominantly inherited microcephaly and developmental delay

Joanne Trinh[1] · Irina Hüning[2] · Zafer Yüksel[3] · Nadja Baalmann[2] · Sophie Imhoff[1] · Christine Klein[1] · Arndt Rolfs[3,4] · Gabriele Gillessen-Kaesbach[2] · Katja Lohmann[1]

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Abstract

Approximately 1–3% of children have intellectual disability or global developmental delay. Heterozygous mutations have emerged as a major cause of different intellectual disability syndromes. In severely affected patients, reproductive fitness is impaired and mutations have usually arisen de novo. Massive parallel sequencing has been an effective means of diagnosing patients, especially those who carry a de novo mutation. The molecular diagnosis can be a way to shift from a more phenotype-driven management of the clinical signs to a more refined treatment based on genotype. Here, we report a novel dominantly inherited *KAT6A* missense variant in the C-terminal transactivation domain identified by exome sequencing in a girl and her father. Both had intellectual disability/developmental delay, short stature, microcephaly, and strabismus with the father being mildly affected. We here report the first inherited variant in *KAT6A* and suggest missense variants in *KAT6A* to be associated with an inheritable, milder clinical presentation compared to previously reported de novo, truncating mutations in this gene.

Introduction

Dominant, heterozygous de novo mutations have emerged as a major cause of different intellectual disability syndromes and are responsible for up to 40% of severe intellectual disability [1]. Recently, de novo truncating mutations in histone K(lysine) acetyltransferase KAT6A (also known as monocytic leukemia zinc finger protein [MOZ]) have been found to be associated with hypotonia, intellectual disability, feeding difficulties, strabismus, oromotor difficulties, microcephaly, craniosynostosis, and cardiac defects in combination with facial dysmorphism [2, 3]. Previous exome sequencing studies have also identified *KAT6A* as a candidate [4–7]. Most previously reported mutations reside in the C-terminal transactivation domain. In this study, we report a father and daughter carrying a missense variant in *KAT6A* with a milder clinical phenotype.

Case report

We report a 10-year-old German girl, born prematurely after 32 weeks of gestation, due to premature rupture of membranes. She is the first child of non-consanguineous German parents (Fig. 1, Supplementary Fig. 1). The body measurements after birth were: weight 1900 g (+0.4 SD), length 41 cm (−0.4 SD), head circumference 30 cm (+0.2 SD). After birth, constriction rings around the right leg and around the digits 2, 3, and 4 of the right hand as well as club feet were noted. Amniotic band were visible on the right hand, thus the diagnosis amniotic band sequence was made

These authors contributed equally: Joanne Trinh, Irina Hüning, Gabriele Gillessen-Kaesbach, Katja Lohmann.

These authors share first authorship: Joanne Trinh, Irina Hüning.

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✉ Irina Hüning
irina.huening@uksh.de

[1] Institute of Neurogenetics, University of Lübeck, 23538 Lübeck, Germany

[2] Institut für Humangenetik, Universität zu Lübeck, 23538 Lübeck, Germany

[3] Centogene AG, Institute for Rare Diseases, 18057 Rostock, Germany

[4] Albrecht Kossel Institute for Neuroregeneration, University Hospital Rostock, 18057 Rostock, Germany

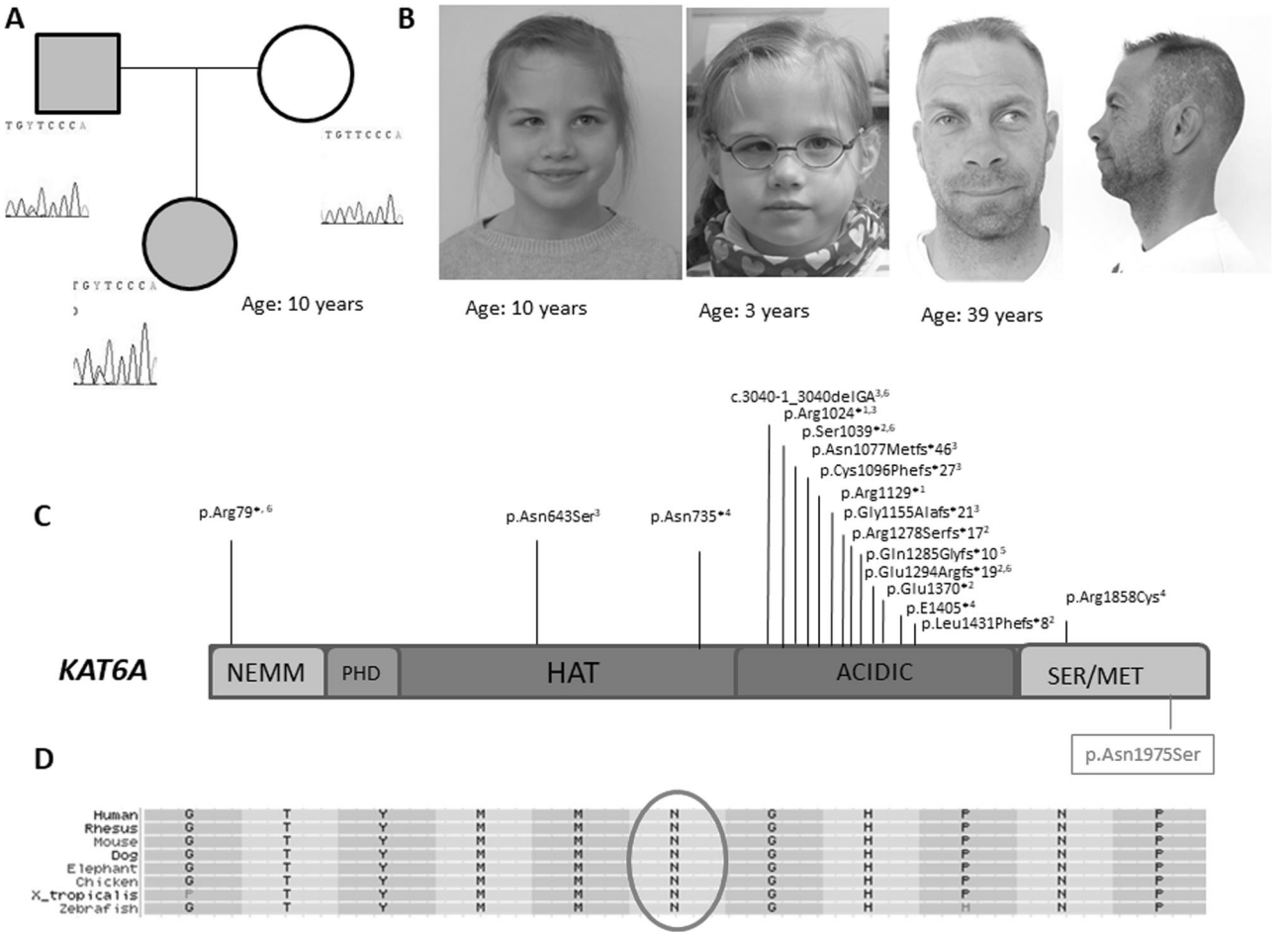

Fig. 1 Dominant KAT6A p.N1875S variant. **a** Pedigree of trio with electropherogram of Sanger sequencing. Index patient and father is affected (filled-in symbols). Heterozygous *KAT6A* c.5924A>G variant **b** Photographs of patient and her father. **c** Domains of the KAT6A protein and location of novel variant reported in this study (red font and outline) and previously reported mutations (Superscript 1: Arboleda et al. [2], 2: Tham et al. [3], 3: Millan et al. [6], 4: DDD study [4], 5: Murray et al. [7], 6: Zwaveling-Soonawala et al. [9]). Color-coded domains include NEMM: nuclear localization domain, PHD: double-plant homeodomain finger, HAT: histone-acetyltransferase domain (also known as MYST domain), ACIDIC: acidic glutamate/aspartate-rich domain, and SER/MET: serine and methionine-rich transactivation domain. **d** Sequence alignment of the amino acid residue (outlined in red) shows high conservation across different species, data source is generated from UCSC

(Supplementary Fig. 1). In the first year of life the patient showed developmental delay. She was able to sit independently at age 1 year, walking was possible at the age of 3.5 years. At around 3 years short stature and microcephaly were documented. Her speech development was severely delayed with lack of expressive language at age of 4 years and severely affected language comprehension. The patient underwent several surgical treatment of her severe club feet deformity. She showed muscular hypotonia and severe obstipation since birth. She presents with strabismus and Duane anomaly. Clinical examination at the age of 10 years showed intellectual impairment, short stature, borderline microcephaly, ophthalmologic abnormalities (strabismus and Duane anomaly), obstipation (less severe than in early childhood), as well as limb deformities due to amniotic band constrictions. The body measurements at age of 10 years were height 127.5 cm (−2.1 SD), weight 30 kg (−0.7 SD), and head circumference 50.5 cm (−1.8 SD).

The intelligence was tested at the age of 8 years with the SON intelligence test (Snijders-Oomen Nonverbal Intelligence Test) with the result of a SON IQ of 53.

The father of the index patient (Fig. 1) was diagnosed with hypotonia, mild global developmental delay, and short stature in early childhood. Also microcephaly, dysmorphic features such as upslanting palpebral fissures, thin upper lip, broad nasal tip, bilateral single palmar creases, as well as ophthalmologic abnormalities (divergent strabismus, posterior synechia, and microphthalmia of the left eye) were documented. Skeletal survey showed delayed bone age of 1 year at chronological age 2.5 years

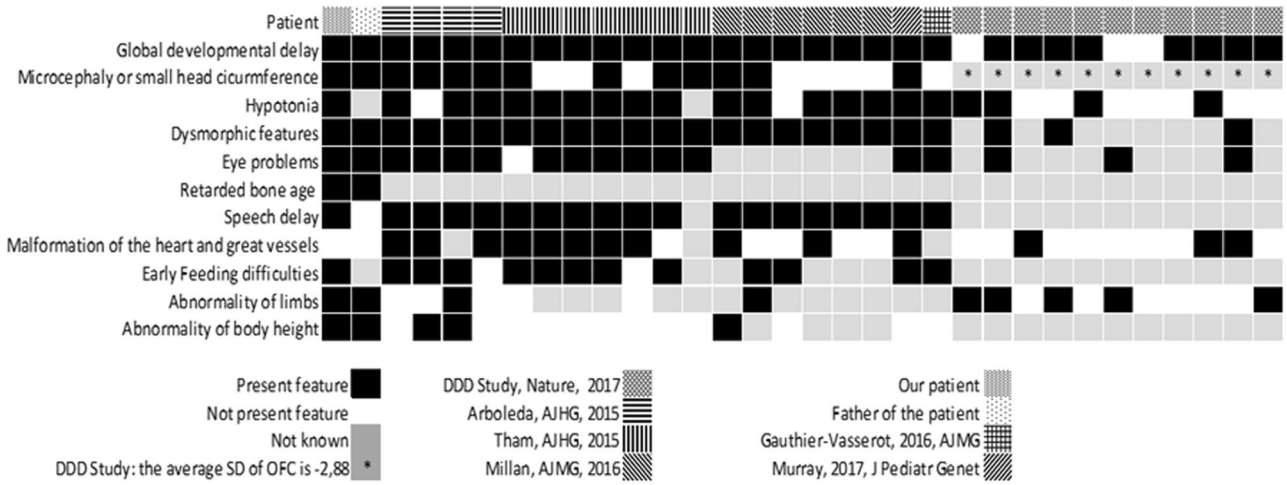

Fig. 2 Patient characteristic comparison across studies. SD standard deviation, OFC occipito-frontal circumference

and hypoplastic first ribs. The body measurements at age 2.5 years were: height 76.5 cm (−4.3 SD), weight 9.78 kg (−2.5 SD), head circumference 46 cm (−3.4 SD). He was treated with growth hormone at age 9–11 years. The father has completed elementary school. He works as a car wash professional. His body measurements (at the age of 39 years) were: height 157 cm (−3.0 SD), weight 51 kg (BMI 20.7 kg/m^2), and head circumference 52 cm (−2.6 SD). He reported no impairment concerning his vision, although no recent ophthalmologic evaluation has been performed. Constipation was not reported. The patient suffered from unilateral inguinal hernia and carpal tunnel syndrome during the past 2 years. At age 38 years, latent epilepsy was diagnosed in EEG after a syncope without the clinical manifestation of seizures. Currently, treatment with lamotrigine and levetiracetam has been performed. The now 28-year-old mother is healthy and has no history of developmental delay.

Genetic analysis

Trio-exome sequencing was performed in the index patient, her affected father and her unaffected mother, for which the parents gave written informed consent. Prior to exome sequencing, conventional cytogenetic analysis showed normal female karyotype 46,XX in the index patient and Array-CGH analysis revealed no evidence for relevant deletions or duplications. Conventional karyotyping was performed in the father during childhood, showing normal male karyotype 46, XY. Exome capture was carried out with Illumina's Nextera Rapid Capture Exome Kit followed by massively parallel sequencing on a NextSeq500 Sequencer (Illumina, San Diego, CA, USA). Downstream bioinformatics analysis was performed as previously described [8]. After applying filtering criteria of exonic or splicing variants, shared by the father and the daughter, with a read number >15, resulting in a protein sequence change, rare in ExAC (<0.001 minor allele frequency) or 1000 genomes, recognized by more than one of three variant callers, with a CADD score >10 and GERP score >3, we identified 37 candidate variants (Supplementary Fig. 2 and Supplementary Table 1). Among these 37 gene candidates, *KAT6A* was the only one that has previously been linked to a neurodevelopmental disease. The *KAT6A* variant (c.5924A>G, p.N1975S) was confirmed by Sanger sequencing in the index patient and her father. Their clinical signs and symptoms accorded with the reported phenotype of *KAT6A* mutation carriers, including global developmental delay, speech delay, hypotonia, and strabismus [1–7, 9] (Fig. 2, Supplementary Table 2). KAT6A p. N1975S is located in the C-terminal transactivation domain of the protein and the asparagine residue at position 1975 is also highly conserved (GERP score 5.93) (Fig. 1). Further, the number of observed missense variants in *KAT6A* in the database of the Exome Aggregation Consortium (ExAC) is lower than expected (z-score = 2.14) [10] underlining a disease-related role of missense variants in this gene. Applying the ACMG recommendations [11], we have scored *KAT6A* c.5924A>G (p.N1975S) as a variant of unknown significance (PM1: it is located in the C-terminal transactivation domain of the protein, PP1: there is co-segregation within the family, and PP3: multiple lines of bioinformatics tools predicts the amino acid change as damaging). We were strict in applying the evidence of pathogenicity and did not take PM2 (absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or ExAC) as a criteria for pathogenicity as the variant is now present in 1 out of 122,999 individuals in GnomAD. This individual may also have mild intellectual impairment but was not excluded from the GnomAD database as only individuals with severe pediatric diseases have been excluded.

Discussion

In this report, we describe the first inherited missense variant in *KAT6A* that likely causes developmental delay, intellectual impairment, short stature, microcephaly and strabismus in the index patient, and a less severe phenotype in the father. In comparison to the previous described patients with truncating, de novo mutations, the phenotype in our patients were milder.

We performed a literature review and database search for individuals carrying reported mutations in *KAT6A* (Table 1, Fig. 2). To date, detailed clinical phenotyping has been reported for de novo variants only including nine truncating, seven frame-shift, one deletion, and two missense mutations [1–7, 9] (Fig. 1). All patients presented with global developmental delay, speech delay, craniofacial abnormalities, and eye problems. Although we could not distinguish the mutation carriers and the respective phenotypes in the large-scale de novo mutation study [4], the composite phenotypic figure shows that 8 out of 11 patients have global developmental delay. Overlapping features such as hypotonia and abnormal axial skeletal morphology are present in some *KAT6A* variant carriers [1–7, 9].

One limitation of our study is that there are 36 additional candidate variants and we cannot fully exclude that one of these changes contributes to the phenotype since additional family members were not available for testing. KAT6A protein forms a part of the histone acetyltransferase complex and acetylates lysine-9 residues in histone H3 (H3K9). Acetylated H3K9 is associated with transcriptionally active genes, and deacetylation is associated with transcriptional silencing. The complex can regulate Hox genes during early developmental stages [12]. Hox genes are choreographers of neurodevelopment and limb formations. Mutations in Hox genes have been implicated in synpolydactyly and hand-foot-genital syndrome [13, 14] and necessary for neural stem cell renewal, normal development of hematopoietic system, and skeletal system for rodents and zebrafish in a dosage-dependent manner [12, 15–17]. Functionally, H3K9 acetylation was decreased and H3K18 acetylation was increased in histone extracts of patient fibroblasts [2].

Many genetic syndromes are caused by mutations in histone acetyltransferases. Some common clinical features of histone acetyltransferase mutations in neurodevelopmental syndromes include global developmental delay and craniofacial dysmorphism, congenital heart defects, feeding disorder, hypotonia [2]. We have identified a novel inherited missense variant in *KAT6A* that likely causes a developmental disorder with variable expressivity. Unlike some of the reported *KAT6A* mutation carriers, both patients in our study did not present with dystonia or congenital heart defects. Further, the father did not show severe intellectual impairment, clubfoot deformity, and obstipation, which are present in his daughter, thus showing the intra-familial variability. Understanding the mechanism of H3K9 acetylation might help find a therapeutic approach to reduce developmental delay in individuals with *KAT6A* mutations. Drugs that inhibit histone deacetylase (HDAC) activity are currently being studied as a therapeutic approach in cancer, neurodegeneration, and developmental diseases [18]. Although therapeutics can be explored for histone acetylase activity, further functional studies examining the exact effect of KAT6A c.5924A>G (p.N1975S) on protein function and animal models should first be explored to precisely determine whether it is pathogenic or not.

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Compliance with ethical standards

Conflict of interest Drs. Yüksel and Rolfs are employees of Centogene AG. The remaining authors declare that they have no conflict of interest.

References

1. Gilissen C, Hehir-Kwa JY, Thung DT, van de Vorst M, van Bon BW, Willemsen MH, et al. Genome sequencing identifies major causes of severe intellectual disability. Nature. 2014;511:344–7.
2. Arboleda VA, Lee H, Dorrani N, Zadeh N, Willis M, Macmurdo CF, et al. De novo nonsense mutations in KAT6A, a lysine acetyl-transferase gene, cause a syndrome including microcephaly and global developmental delay. Am J Hum Genet. 2015;96:498–506.
3. Tham E, Lindstrand A, Santani A, Malmgren H, Nesbitt A, Dubbs HA, et al. Dominant mutations in KAT6A cause intellectual disability with recognizable syndromic features. Am J Hum Genet. 2015;96:507–13.
4. Deciphering Developmental Disorders Study. Prevalence and architecture of de novo mutations in developmental disorders. Nature. 2017;542:433–8.
5. Gauthier-Vasserot A, Thauvin-Robinet C, Bruel AL, Duffourd Y, St-Onge J, Jouan T, et al. Application of whole-exome sequencing to unravel the molecular basis of undiagnosed syndromic congenital neutropenia with intellectual disability. Am J Med Genet A. 2017;173:62–71.
6. Millan F, Cho MT, Retterer K, Monaghan KG, Bai R, Vitazka P, et al. Whole exome sequencing reveals de novo pathogenic variants in KAT6A as a cause of a neurodevelopmental disorder. Am J Med Genet A. 2016;170:1791–8.
7. Murray CR, Abel SN, McClure MB, Foster J 2nd, Walke MI, Jayakar P, et al. Novel causative variants in DYRK1A, KARS, and KAT6A associated with intellectual disability and additional phenotypic features. J Pediatr Genet. 2017;6:77–83.
8. Trujillano D, Bertoli-Avella AM, Kumar Kandaswamy K, Weiss ME, Koster J, Marais A, et al. Clinical exome sequencing: results from 2819 samples reflecting 1000 families. Eur J Hum Genet. 2017;25:176–82.
9. Zwaveling-Soonawala N, Maas SM, Alders M, Majoie CB, Fliers E, van Trotsenburg ASP, et al. Variants in KAT6A and pituitary anomalies. Am J Med Genet A. 2017;173:2562–5.

10. Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature. 2016;536:285–91.
11. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24.
12. Voss AK, Collin C, Dixon MP, Thomas T. Moz and retinoic acid coordinately regulate H3K9 acetylation, Hox gene expression, and segment identity. Dev Cell. 2009;17:674–86.
13. Goodman FR, Bacchelli C, Brady AF, Brueton LA, Fryns JP, Mortlock DP, et al. Novel HOXA13 mutations and the phenotypic spectrum of hand-foot-genital syndrome. Am J Hum Genet. 2000;67:197–202.
14. Goodman FR, Scambler PJ. Human HOX gene mutations. Clin Genet. 2001;59:1–11.
15. Thomas T, Corcoran LM, Gugasyan R, Dixon MP, Brodnicki T, Nutt SL, et al. Monocytic leukemia zinc finger protein is essential for the development of long-term reconstituting hematopoietic stem cells. Genes Dev. 2006;20:1175–86.
16. Crump JG, Swartz ME, Eberhart JK, Kimmel CB. Moz-dependent Hox expression controls segment-specific fate maps of skeletal precursors in the face. Development. 2006;133:2661–9.
17. Miller CT, Maves L, Kimmel CB. Moz regulates Hox expression and pharyngeal segmental identity in zebrafish. Development. 2004;131:2443–61.
18. Falkenberg KJ, Johnstone RW. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. Nat Rev Drug Discov. 2014;13:673–91.