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ORIGINAL ARTICLE

Clinical features and underlying mechanisms of KAT6B disease in a Chinese boy

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Abstract

Background: Lysine acetyltransferase 6B (KAT6B) encodes a highly conserved histone acetyltransferase that regulates the expression of multiple genes and is essential for human growth and development.

Methods: We identified a novel frameshift variant c.3185del (p.leu1062Argfs*52) in a 5-year-old Chinese boy and further analyzed *KAT6B* expression and its interacting complexes and downstream products using real-time quantitative polymerase chain reaction (qPCR). Furthermore, we assessed its three-dimensional protein structure and compared the variant with other reported *KAT6B* variants.

Results: The deletion changed the leucine at position 1062 into an arginine, resulting in translation termination after base 3340, which may have affected protein stability and protein–protein interactions. *KAT6B* mRNA expression levels in this case were substantially different from those of the parents and controls in the same age range. There were also significant differences in mRNA expression levels among affected children's parents. RUNX2 and NR5A1, downstream products of the gene, affect the corresponding clinical symptoms. The mRNA expression levels of the two in children were lower than those of their parents and controls in the same age range.

Conclusion: This deletion in *KAT6B* may affect protein function and cause corresponding clinical symptoms through interactions with key complexes and downstream products.

KEYWORDS
Chinese children, deletion variant, downstream products, interactant, *KAT6B*

Xiaoang Sun and Xiaona Luo have contributed equally to this work and share first authorship.

1 | BACKGROUND

Lysine acetyltransferase 6B (KAT6B; OMIM 605880) proteins currently constitute the largest and most diverse family across different histone acetyltransferase (HAT) families (Jiang et al., 2021; Shanmugam et al., 2021). Currently, the family includes five human HATs, namely Tip60, MOZ, MORF, HBO1, and MOF, which are known as lysine acetyltransferases (KATs; Lemire et al., 1993). Epigenetic regulation by histone acetylation is critical to normal growth and development, and its role in human genetic diseases is increasingly recognized. The acetylation of histones by KAT is essential for gene expression, DNA repair, and cell cycle homeostasis regulation (McCullough & Marmorstein, 2016). KAT6B encodes a highly conserved HAT and forms multi-subunit complexes with other proteins, including KAT6A (OMIM 605880), BRPF1 (OMIM 602410), and ING5 (OMIM 608525; Yang, 2015). KAT6B (MYST4/MORF) acetylates histone 3 (H3) by forming a stable complex with the tumor suppressor ING5 and bromodomain PHD finger proteins 1/2/3, thereby remodeling *KAT6B* chromatin. It also regulates the expression of multiple genes (Kraft et al., 2011).

The prevalence of *KAT6B* disease remains unknown. Out of the 89 patients with *KAT6B* disease reported to date, 18 had genitopatellar syndrome (GPS), 58 had Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS), and 13 were described as having an intermediate phenotype (Lemire et al., 1993). GPS and SBBYSS disease mechanisms are associated with gain-of-function and loss-of-function variants (Campeau, Kim, et al., 2012; Campeau, Lu, et al., 2012), respectively; however, these have not been experimentally tested. Pathogenic variants include a spectrum of nonsense, missense, splice site, and predicted frameshift variants. The *KAT6B* pathogenic variant spectrum from previously published individuals includes 56 variants: 22 substitutions, 22 minigenic deletions, 10 minigenic duplications, and 2 insertion-related minigenic deletions (Zhang et al., 2020). Variation at the protein level included 33 frameshifts, 19 nonsense, 2 missense, and 2 splicing defects. GPS-SBBYSS-associated variants are most often located in exon 18, the last exon of the gene (Lonardo et al., 2019). In addition, more disease-associated proximal variants in exons 3, 7, 11, and 14–17 have been documented.

Here, we describe a male Han patient with clinical features of KAT6B disease (growth retardation and characteristic facial features). Next-generation sequencing of the patient's whole exome revealed a deletion variant in *KAT6B*. We speculate that this variant is likely pathogenic and related to the patient's clinical characteristics. Its three-dimensional (3D) structure and related pathogenic mechanisms were also explored.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

The study was reviewed and approved by the Ethics Committee of Shanghai Children's Hospital. Written informed consent forms were signed by the patient's parents (including permission to publish photos) and the legal guardians of a sex- and age-matched control group (including collecting blood samples for genetic analysis).

2.2 | Variation detection

Genomic DNA was isolated from participants' blood samples obtained via the peripheral veins of the children and their parents, and genomic DNA was sheared using the Covaris Ultra Sonicator (Covaris, Inc.). Genomic DNA was then hybridized into an array containing Roche NimbleGen 2.0 probe sequences to obtain an exon-rich DNA library. We then used an Illumina TruSeq DNA sample preparation kit to pre-capture the library and laser-capture microdissection (LCM) and polymerase chain reaction (PCR; LCM-PCR) to amplify and analyze it. The presence of variants identified by whole-exome sequencing was further confirmed by PCR Sanger sequencing of DNA samples from patients and their parents (Luo et al., 2021; Wang et al., 2020, 2021).

2.3 | Real-time quantitative PCR analysis of *KAT6B* expression and its interacting complexes

Total RNA was extracted from fresh blood using an RNA extraction kit (YEASEN Biotech Co., Ltd.) according to the manufacturer's instructions. The concentration and purity of the total RNA were detected using a nucleic acid–protein analyzer. Subsequently, cDNA was synthesized using the total RNA as the template for reverse transcription according to the manufacturer's instructions for the reverse transcription kit (Takara Shuzo Co., Ltd., Appendix S1 and S2). RT-qPCR was performed using SYBR Premix Ex Taq II (Tli RNase H Plus; Takara Shuzo Co. Ltd.) and LightCycler® 96 instrument (Roche Inc.). After an initial denaturation of 3 min at 95.0°C, the reaction was cycled 35 times for 30 s at 95.0°C and 45 s at 60.0°C. Transcript levels were determined from triplicate samples and expressed as mean ± standard error of the mean. Statistical analyses of the qPCR data were performed using the 2-DDCt method to compare the mean values of the samples. Asterisks

indicate statistically significant differences (Student's *t*-test, $^{**}p < 0.05$, $^{***}p < 0.01$).

2.4 | Genetic pathogenicity assessment

The deletions were considered in at least two silico software (Mutation Taster; RRID: SCR_010777 and SIFT RRID: SCR_012813) and assigned a high pathogenicity score (disease-causing pro = 1; SIFT score < −2.5).

2.5 | Protein structure prediction using the I-TASSER server for deletion variants

We used I-TASSER software to input the FASTA format of related proteins to obtain the 3D structure of the gene. The server is available at http://zhanglab.ccmb.med.umich.edu/I-TASSER.

2.6 | Distribution of variants in *KAT6B*

We mapped the locations of newly deleted variants to their corresponding domains and analyzed the distribution of the other 86 variants.

3 | RESULTS

3.1 | Clinical case

A 5-year-old Chinese boy presented to the Department of Neurology, Shanghai Children's Hospital, because of developmental delay. His parents reported that he did not sit or stand without aid until he was 18 months old. He was now finally able to understand instructions but could only speak in very simple terms, such as "mom," "dad," and other simple phrases.

Physical examination revealed a downward sloping palpebral fissure, a broad and flat nasal bridge, a bulbous nasal tip, a thin upper lip, a micromandibular chin (Figure 1a,b), long toes (Figure 1c,d), and an inability to flex the thumb and ring finger to 90°. His height was 103 cm (within the third percentile of children of the same age and sex), and his weight was 15.5 kg. His brain magnetic resonance imaging (MRI) results from another hospital showed no abnormality and his hearing was normal; however, his IQ was 46, reflecting moderate intellectual disability. The child had atrial septal defect 6 months after birth, which was cured after age 1; cryptorchidism was found at birth, and surgery was performed at age 1 for corrective purposes.

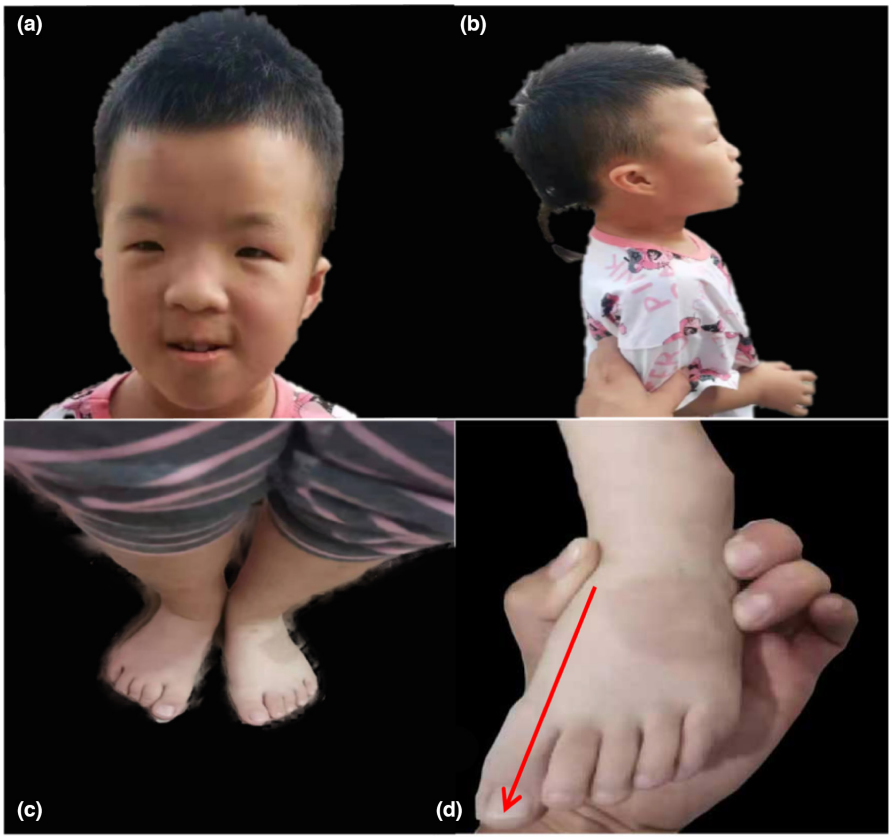

FIGURE 1 (a–d) Clinical features of the child. (a, b) The child has slight facial deformity features: a downward sloping palpebral fissure, a broad and flat nasal bridge, a bulbous nasal tip, a thin upper lip, and a micromandibular chin. (c, d) The child has long toes.

3.2 | Variation detection

The exon test results of the patient in our hospital suggested a novel frameshift variant in *KAT6B*: NM_012330.4:c.3185del:p.(leu1062Argfs*52). The proband was found to be heterozygote and both parents of the patient were wild-type. The variant is rare and has not been previously reported in the Exome Aggregation Consortium, ESP, or 1000G databases (MAF = 0). According to the American Society of Medical Genetics and Genomics (ACMG, RRID: SCR_005769) standards for interpreting sequence variations, the novel *KAT6B* variant identified here is pathogenic.

3.3 | RT-qPCR analysis of *KAT6B* expression and its interacting complexes

KAT6B forms complexes with ING5, BRPF1/2/3, and MEAF6 (OMIM 611001). The transcription level of *KAT6B* in the family was analyzed with RT-qPCR using RNA extracted from whole blood and *KAT6B*-specific primers. *KAT6B* mRNA expression levels in the patient were significantly different from those in the patient's parents and children of different sexes (Figure 2a). Regarding the *BRPF1*, *BRPF2* (OMIM 604589), and *ING5* expression levels, the mRNA expression levels of the child were lower than those of his parents and children of different sexes in the same age range ($p < 0.01$; Figure 2b–d). There were no marked difference in *BRPF3* (OMIM 616856) and *MEAF6* expression levels. The downstream genes of *KAT6B* are *RUNX2* (OMIM 600211) and *NR5A1* (OMIM 184757). The mRNA expression levels of the genes in the patient were significantly different from those of his parents and children of different sexes in the same age range ($p < 0.01$; Figure 2e,f).

3.4 | Deletion variant results in changes in protein function and structure

Owing to the variant at the c3185del site in *KAT6B*, the leucine at position 1062 was changed to arginine, effectively terminating translation. We compared the 3D structure of the wild-type (Figure 3a). Amino acid changes may affect the intrinsic protein stability of the system and its protein–protein interactions (Figure 3b).

3.5 | Distribution of variants in *KAT6B*

There were 77 disease-causing genes (89.5%) distributed between 1000 and 2000 amino acids, including the novel deletion variants we identified (Figure 4).

4 | CONCLUSIONS

The mutation proposed in the present study has not been documented in previous studies. The disease caused by all the related gene variants may be named KAT6B disease in the future. The most common clinical phenotypes are currently reported as GPS and SBBYSS; however, some studies suggest that this reflects only a part of the *KAT6B* disease spectrum. Although the clinical manifestations of the two clinical phenotypes overlap, they still retain their unique clinical characteristics. The main clinical features of children with GPS include the following: genital abnormalities (in women: clitoral hypertrophy and/or hypoplasia of labia minora or majora; in men: cryptorchidism and scrotal hypoplasia), patellar hypoplasia/hypoplasia, flexion contractures of the hips and knees (including clubfoot), corpus callosum hypoplasia with microcephaly, and hydronephrosis and/or multiple renal cysts. Key clinical features in children with SBBYSS are as follows: long thumb/big toe, immobile mask-like face, palpebral fissure/upper eyelid sagging, tear duct abnormalities, and patellar hypoplasia/hypoplasia (Gannon et al., 2015; Yabumoto et al., 2021). The patient in our study had distinct facial features, such as ptosis of the palpebral fissure, enlarged toes, and a history of cryptorchidism at birth, resembling the SBBYSS phenotype.

To date, the known deleterious *KAT6B* variants mainly affect exons 16–18 of the acidic and serine/methionine domains (Brea-Fernandez et al., 2019; Wiesel-Motiuk & Assaraf, 2020). The number of variants across different *KAT6B* domains vary. The protein encoded by this gene has a total of 2074 amino acids, and the pathogenic genes are mostly distributed between 1000 and 2000 amino acids. In the patient described here, the 3185th base was deleted, causing the leucine corresponding to the 1062nd position to change to an arginine, resulting in the termination of translation after the 3340th base, with the 1062nd amino acid located at the 16th exon. In addition, an experiment confirmed that the KAT6B expression level in the child was significantly lower than that in his parents and healthy children of different genders. This indicates that the variant may lead to a reduction in KAT6B expression, ascribable to deletion variant and the generation of premature termination codon (PTC), which subsequently results in the premature termination of peptide chain synthesis and formation of non-functional or incomplete proteins or nonsense-mediated mRNA decay (NMD) through the identification and degradation of PTC-containing transcripts to prevent potential toxicity (Wiesel-Motiuk & Assaraf, 2020). This copy number loss makes such variants pathogenic. Protein function still requires further assessment and validation; however, we cannot carry

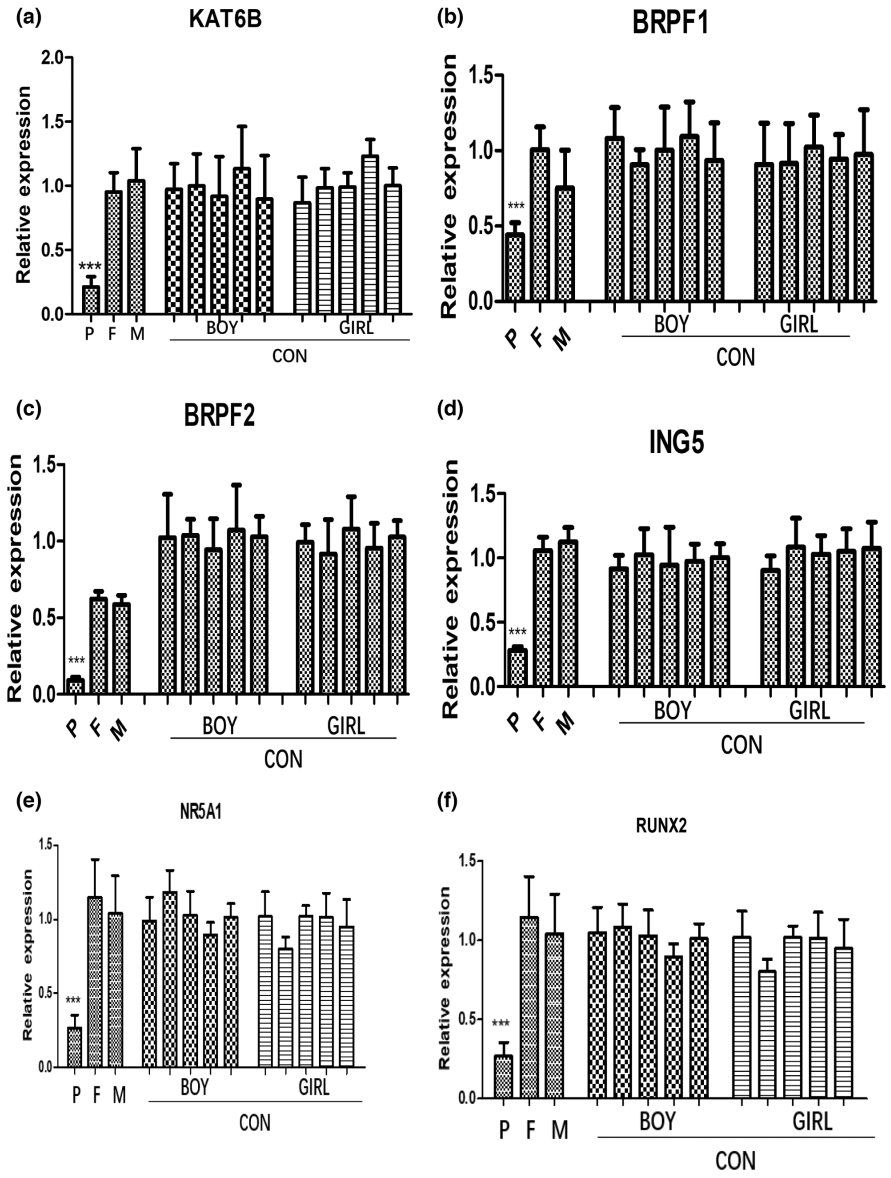

FIGURE 2 (a) Real-time quantitative polymerase chain reaction experiments were performed for *KAT6B* mRNA expression in the patient's nuclear family. *KAT6B* mRNA expression levels in patients were significantly different from those of their parents and normal children of different sexes. (b–d) The mRNA expression of the interacting complexes were analyzed. The *BRPF1*, *BRPF2* and *ING5* expression levels in the children were significantly different from those of their parents and healthy children of different sexes. (e, f) The mRNA expression of the downstream genes *RUNX2* and *NR5A1* were analyzed. *RUNX2* and *NR5A1* mRNA expression levels in patients were significantly different from those of their parents and healthy children of different sexes. ***$p < 0.01$.

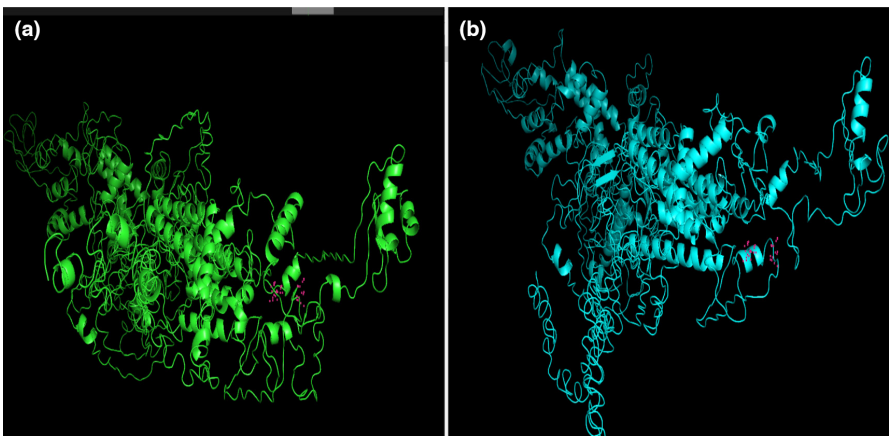

FIGURE 3 (a) The three-dimensional (3D) atomic model based on KAT6B sequence from wild-type generated by iterative threading assembly refinement server. (b) The 3D atomic model based on protein sequence from the deletion variant of NM_012330.4:c.3185del:p.(leu1062Argfs*52) in KAT6B generated by the iterative threading assembly refinement server.

out such experiments at this time because of insufficient blood sample volume.

KAT6B is highly expressed in adult neural stem cells and plays key roles in various developmental processes, including neurogenesis and skeletal development (Yang & Ullah, 2007). Kraft et al. (2011) also observed that genes in the MAPK signaling pathway were downregulated in *KAT6B* knockout cell lines and *KAT6B*-deficient mice,

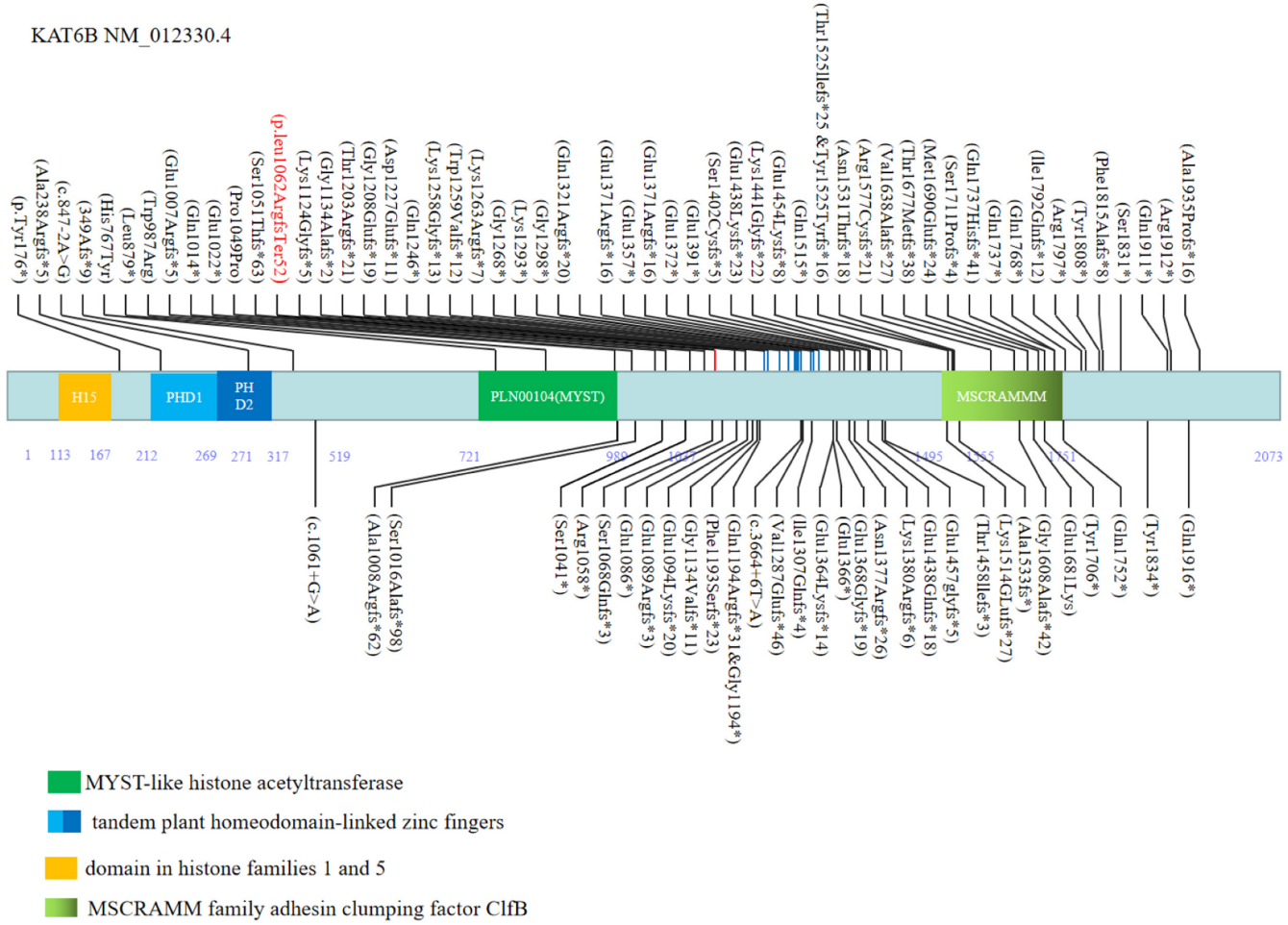

FIGURE 4 Distribution of pathogenic variants in KAT6B. The novel pathogenic variants in our study are shown in red; previously reported variants are displayed in black.

thereby affecting gene transcription, suggesting that *KAT6B* plays an important role in the regulation of cell cycle and differentiation. Therefore, defects in *KAT6B* can lead to intellectual disorders. The children we reported also came to our hospital because of growth retardation. Furthermore, the position of a *KAT6B* variant is thought to result in different syndromes. Some studies have suggested that variants in exon 16 often lead to the SBBYSS phenotype, consistent with the characteristics of our reported cases.

KAT6B contains several acetylated subunits: MORF (also known as MYST4 and KAT6B), ING5, BRPF1/2/3, and EAF6. The BRPF family includes BRPF1, BRPF2, and BRPF3, which are scaffolding proteins for the *Myst* HAT (Klein et al., 2014). They interact with *Myst* HAT to enhance its acetyltransferase activity and transcriptional activation potential, thereby regulating embryonic development. *BRPF1* may encode a chromatin regulator that can promote protein acetylation by binding to other regulatory proteins, such as growth protein inhibitor 5 (ING5) and MYST/ESA1 associated factor 6 (MEAF6; Lonardo et al., 2019). It has been suggested that *BRPF1* is critical for the development of the cerebral cortex and hippocampus and plays a key role in various developmental processes. For example, it is important for the development of hematopoietic and neural stem cells. Moreover, *BRPF1* can affect the development of the dentate gyrus by regulating neural stem cells (You et al., 2015). This study found that *BRPF1* expression was reduced in children with *KAT6B* deficiency, which is one of the reasons underpinning growth retardation in children (Yan et al., 2017). This may be related to the interaction between *KAT6B* and *BRPF1*, resulting in defective histone H3K23 acetylation. The reduced *BRPF1* and *BRPF2* expression levels may be due to deletion variants that decrease *KAT6B* expression. Although the *BRPF2* and *BRPF3* sequences are highly similar to that of *BRPF1*, the complexes they preferentially form do not include *KAT6B*; therefore, their functions differ from those of *BRPF1* at the molecular level (Mishima et al., 2011; Yang, 2015). *BRPF2* is more likely to be involved in fetal erythropoiesis and thymocyte development (Cho et al., 2020), while *BRPF3* function has

been relatively less documented. Some studies have also suggested that *BRPF3* has potential functions in tissues it is highly expressed such as the adult testis and brain; however, further exploration and analysis are required. Furthermore, inactivation of *BRPF2* causes growth retardation, while *BRPF3* is not required for normal growth and development. Studies have shown that the lack of *BRPF3* neither leads to obvious phenotypes nor causes changes in the transcriptional levels of *BRPF1* and *BRPF2* (Yan et al., 2016).

KAT6B is highly expressed in the diaphysis and patella of long bones. *KAT6B* interacts with *RUNX2*, and the C-terminal region of *KAT6B* binds to the transcription factor *RUNX2* (*CBFA1*) in vitro and in vivo (Clayton-Smith et al., 2011); i.e., *RUNX2* is a *KAT6B*-activated transcription factor that regulates osteogenesis (Desh et al., 2014). *RUNX2* is expressed in pluripotent mesenchymal cells, cells of the osteoblast lineage, and chondrocytes, and is essential for osteoblast differentiation and chondrocyte maturation (Komori, 2018, 2020). In the present study, we found that *RUNX2* expression in children was lower than that in other children in other studies. This may be related to the decreased *BRPF1*, *KAT6B*, and *ING5* expression. Because studies have suggested that *BRPF1* and *KAT6B* synergistically enhance *RUNX2*-dependent transcription, low *ING5* expression decreases the ability of *BRPF1* to activate downstream *RUNX2*-dependent transcription, resulting in the inability of children to flex their fingers, and their long toes may be related to the activation of *RUNX2* by a *KAT6B* variant. *RUNX2* forms a heterodimer with *CBFB*, and *RUNX2*/*CBFB* regulates skeletal development by activating multiple signaling pathways and engaging in their mutual regulation.

Some scholars have proposed that *NR5A1* may explain the genital abnormalities found in children with GPS (Campeau, Kim, et al., 2012; Campeau, Lu, et al., 2012; Schlaubitz et al., 2007). *NR5A1* is expressed in both fetal and adult Leydig cells and is a key transcriptional regulator of reproductive development and function-related genes. The same *NR5A1* deficiency has implications for testicular function, as *NR5A1* plays a key role in the transcriptional activation of *INSL3*, a basal Leydig cell product underlying testicular descent (Ferlin et al., 2015; Koskimies et al., 2002; Zimmermann et al., 1998). Children with *NR5A1* variants present with unilateral or bilateral cryptorchidism. Moreover, the qPCR results in the present study suggested that the deletion variant would affect downstream *NR5A1* expression in children with KAT6B disease.

The findings reported here identify a novel *KAT6B* variant and associated pathogenesis. Our work enriches the mutational spectrum of *KAT6B* and increases our understanding of its phenotypes. In practice, clinicians can conduct early genetic testing and routine follow-up for children with growth retardation and special facial features. In the future, we need more research involving protein functional studies and in vitro experiments to investigate the hypothesized molecular mechanisms leading to *KAT6B* disorders.

AUTHOR CONTRIBUTIONS

XS and LL performed laboratory experiments. XS drafted the manuscript. XS and XL analyzed the genomic data. SW、CW and FY analyzed the clinical data and diagnosed patients. LL、XL and JY assisted with the software and methodology. XS performed the validation experiments. YC edited the manuscript. All authors approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

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SUPPORTING INFORMATION

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