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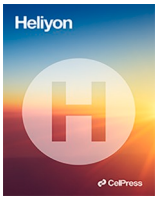

Case report

Novel *KMT5B* variant associated with neurodevelopmental disorder in a Chinese family: A case report

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ABSTRACT

Background: We report here the clinical and genetic features of *KMT5B*-related neurodevelopmental disorder caused by a novel heterozygous frameshift variant in *KMT5B* in a Chinese family.

Case presentation: A 7-year-old Chinese boy with mild-to-moderate intellectual disability, significant language impairment, motor disability, and coordination difficulties presented to our hospital because he "could not speak and did not look at others." He was diagnosed with autism spectrum disorder previously owing to developmental delays in cognition, language expression, and understanding. The child also had variable nonspecific features including macrocephaly, wide button-hole space and nasal bridge, low ear, social behavior disorder, and foot deformities. Exome sequencing (ES) revealed that both the proband and his younger brother had inherited a novel heterozygous frameshift variant c.438_439ins[ASD; KT192064.1:1_310] of the *KMT5B* gene from their father. Bioinformatics analysis showed that the novel mutation affected the structure of the KMT5B pre-SET domain, mainly in the α-helix region. According to the American College of Medical Genetics and Genomics (ACMG) guidelines, this type of variant was eventually determined to be likely pathogenic (PVS1+PM2_P).

Conclusions: Our investigation expands the mutation spectrum of *KMT5B* to help us to better understand *KMT5B*-related neurodevelopmental disorder.

1. Introduction

KMT5B-related neurodevelopmental disorder is an autosomal dominant genetic disorder caused by a mutation in the *KMT5B* gene characterized by macrocephaly and intellectual disability. Additional features include failure to thrive, unique facial and foot features, neurologic behavioural psychiatric problems, absent speech or language deficiency, and development delays with coordination difficulties [1,2]. Patients usually range in age from 5 to 19 years. Children diagnosed with *KMT5B*-related neurodevelopmental disorder also have non-neurological abnormalities with differences in the degree of manifestation, including dysmorphic facial features, cryptorchidism, foot deformities, and sleep difficulties; some even have a tendency toward tall stature, while some patients have febrile seizures and other phenotypes [3–6].

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KMT5B-related neurodevelopmental disorder is caused by heterozygous loss-of-function variants in *KMT5B* on chromosome 11q13.2, and the transcript (NM_017635.5) is composed of 11 exons [7–9]. The human *KMT5B* gene encodes histone-lysine N-methyltransferase KMT5B (NP_060105.3), which mediates H4K20 dimethylation (H4K20me2) and trimethylation (H4K20me3) and plays an important role in diverse cellular processes, including DNA replication, DNA damage response, and DNA repair [3,10,11]. In animal models, the *KMT5B* homologous gene is expressed in the brain prior to the onset of embryonic development. *KMT5B* knock-out mice are embryonic lethal [12,13]. This suggests that KMT5B is essential for the early development of mammals. As a top-ranking high-risk gene, mutations in *KMT5B* have been found in multiple diseases including *KMT5B*-related neurodevelopmental disorder and autism spectrum disorder (ASD). Variation in the *KMT5B*-related neurodevelopmental disorder was previously reported with a variety of cognitive neurodevelopmental disorders associated with heterozygous variants in the *KMT5B* gene [5]. To date, about 170 variants associated with *KMT5B* have been reported in the Human Gene Mutation Database (HGMD), ClinVar Database, and published literature [2,3,9]. Here, we present a case of neurodevelopmental disorder in a Chinese family with a novel heterozygous frameshift variant in *KMT5B* (ClinVar accession number: SCV004231840).

2. Case presentation

The proband was a 7-year-old boy who presented to our hospital with complaints of absent speech and development delays. He did not make eye contact when called out by his name. The proband was the first child of non-consanguineous parents in China and had no

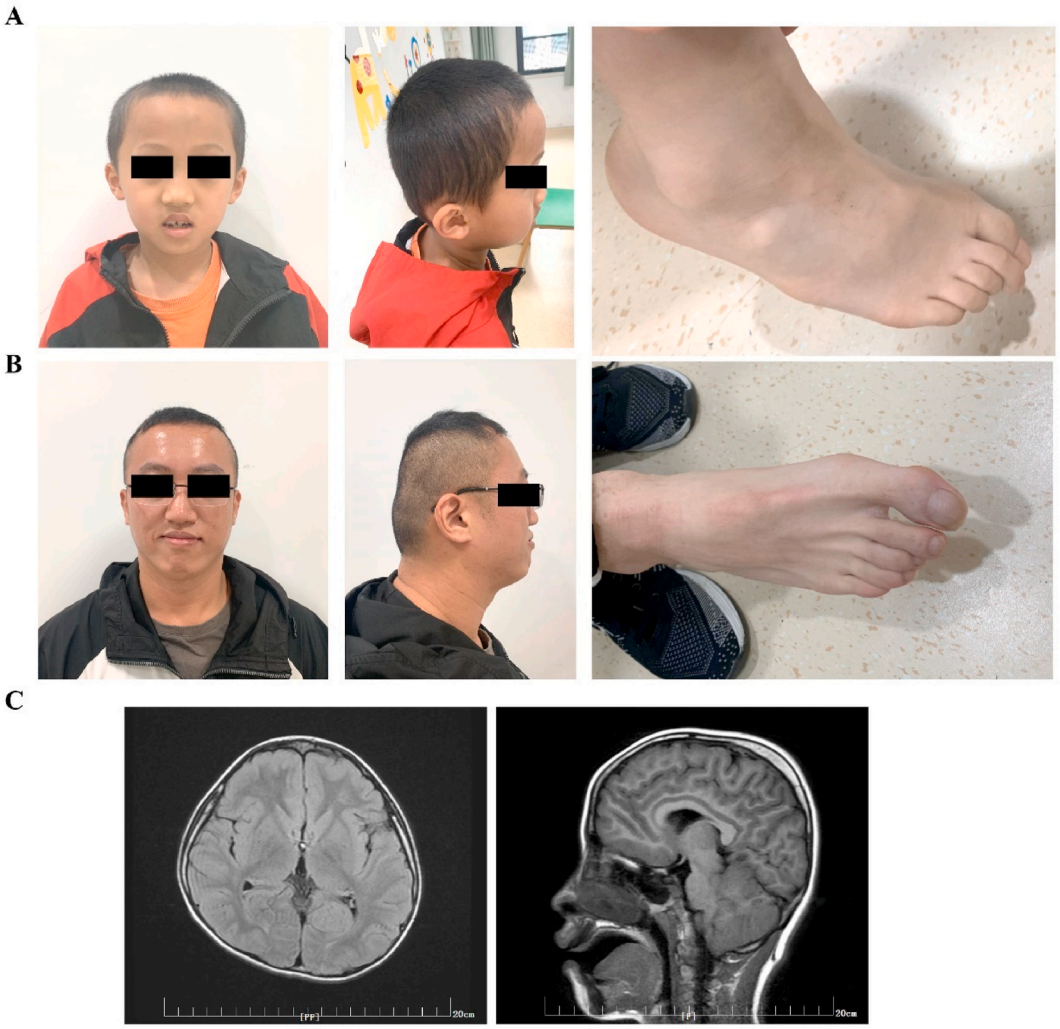

Fig. 1. Clinical and imaging features of the proband. (A) The picture illustrates the facial dysmorphic features of the proband consisting of macrocephaly, wide forehead, wide eye distance, wide nasal bridge, low ear position, long feet, long toes and sparse teeth. (B) The picture demonstrates that the father has similar facial and feet features to the proband. (C) Brain MRI showed no abnormalities were observed in the size and shape of ventricles and cisterns. The mucosa of the right sphenoid sinus was thickened and no obvious abnormalities were observed in the brain parenchyma when the boy was 7 years old.

family history of similar symptoms. There were no significant differences in his prenatal and birth history. He was born via vaginal delivery (weight: 3350 g, length: 50 cm). The Apgar score was 9 at 1 min, 10 at 5 min, and 10 at 10 min after birth. The mother underwent regular prenatal examinations during the pregnancy, and all results were normal. The proband had no significant birth history and was exclusively breastfed without any food or drug allergies.

The proband raised his head at 5 months, rolled over at 7 months, sat at 8 months, and walked at 1 year and 10 months. At the age of 2 years, he was found to have delayed language development, and at 2 years and 11 months, he was found to have severe developmental delays in cognitive and verbal expression after functional assessment. At 3 years and 11 months, the proband was initially diagnosed with ASD on account of having developmental delays with mild-to-moderate intellectual impairment, accompanied by speech problems, motor development delays, and coordination difficulties. At the age of 7 years, he received a comprehensive physical examination. His height was 95 cm (50th–75th percentile), weight was 25 kg (50th–75th percentile), and head circumference was 56.4 cm (>97th percentile). His dysmorphic features included macrocephaly, wide forehead, wide eye distance, wide nasal bridge, low ear position, long feet and toes, disordered social behavior, global developmental delay with mildly delayed walking, intellectual disability, and poor language ability (Fig. 1A). After a few months of speech and occupational therapy training, the proband could watch people occasionally. Sometimes, the proband could respond to the sound of his name, and pronounce monosyllables but could not engage in active speech. Other times, he was unable to cooperate with simple instructions; his attention was quickly diverted, and joint attention could not be elicited. He showed poor eye contact and was not interested in his surroundings, so he had an abnormal social interaction. His blood counts, liver and kidney function tests, and thyroid function tests were normal, and there were no abnormalities in haematuria metabolism and blood ammonia levels. A fat-soluble vitamin test showed that vitamin D levels were lower than normal.

The proband has a younger brother who exhibits similar facial and clinical features, and has been diagnosed with moderate intellectual and developmental disabilities. During the physical examination, it was observed that the younger brother could respond to the sound of his name sometimes, had short eye contact, partially followed simple instructions, exhibited attention diverted quickly, lacked cooperation in joint attention tasks, and displayed poor coordination of limbs.

The father has similar facial and foot features as the proband, including macrocephaly, wide forehead, wide eye distance, wide nasal bridge, low ear position, and long feet and toes (Fig. 1B). The father also showed language and motor developmental delay in his childhood. He could walk at 2 years old and call his mom and dad at 3 years old. However, it seemed that these developmental delay conditions were alleviated to some extent after reaching adulthood. The proband's mother and paternal grandmother said that "the

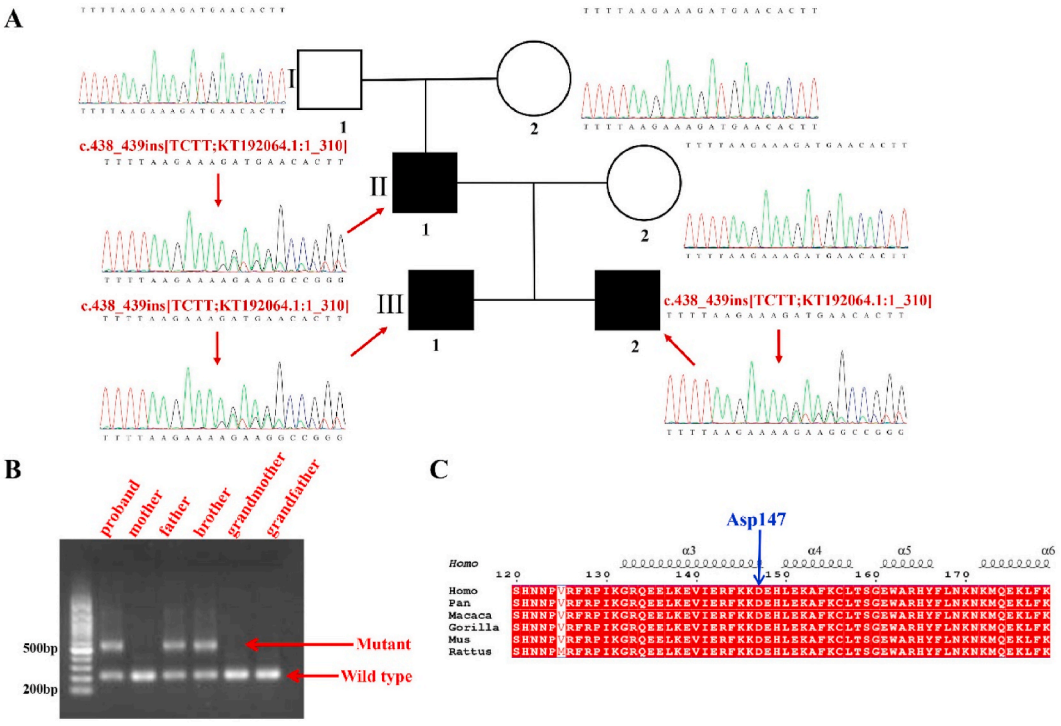

Fig. 2. Identification and analysis of *KMT5B* mutation in this family. (A) The variant c.438_439ins[TCTT; KT192064.1:1_310] was identified by ES in II1, III 1 and III 2. The fully filled symbol in black indicates those affected by *KMT5B*-related neurodevelopmental disorder, and the open symbol indicates those unaffected. Squares represent male, circles represent female specifically. (B) Results were confirmed by Sanger sequencing. (C) Orthologous protein sequence alignment of *KMT5B* from different species. The mutated residue demonstrating conservation of asparagine (Asp) at codon 147 is indicated by the blue arrow. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

father could communicate with others normally." Because no assessments were conducted to evaluate the father's intellectual capacity or language development level, it remains inconclusive whether he still shows indications of developmental delays. We will continue to monitor and follow-up with both the father and the younger brother.

The proband's brain magnetic resonance imaging (MRI) showed no abnormalities in the size and shape of ventricles and cisterns. The mucosa of the right sphenoid sinus was thickened, and no obvious abnormalities were observed in the brain parenchyma (Fig. 1C). Long-term video electroencephalography (EEG) showed no obvious abnormalities. Ophthalmic and hearing assessments were normal. The Autism Behavioural Examination Scale (ABC) score was 55, and the Childhood Autism Rating Scale (CARS) score was 30. A detailed examination of the family history revealed no similar findings in any relative except his younger brother and father.

2.1. Exome sequencing (ES)

To determine the aetiology of the disease, ES was performed with the consent of the proband's family members. The study protocol was approved by the Ethics Committee of Lianyungang Maternal and Child Health Hospital (Project no. LW2023003). Written informed consent was obtained from the proband's parents for the publication of any potentially identifiable images or data included in this article. Genomic DNA was extracted from peripheral venous blood from the family members using a QIAamp DNA Blood Mini kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's protocol. The isolated gDNA samples were randomly fragmented by a Covaris sonicator. They were end-repaired, enriched, and circularized into DNA nanoballs. Subsequently, exome sequencing was performed to comprehensively identify the disease-causing variant using a DNBSEQ-T7 platform (BGI, Shenzhen, China), and the desired average sequencing coverage for each sample was obtained. After data filtering, the clean data of each sample was used for further bioinformatics analysis [14,15]. The ES protocol is mentioned in a previous report [15]; we screened all genetic variants.

2.2. Sanger sequencing

Finally, the frameshift variant c.438_439ins[TCTT; KT192064.1:1_310] in *KMT5B* (NM_017635.5) was evaluated using the American College of Medical Genetics and Genomics (ACMG) guidelines criteria [16] and the human reference genome used was the GRCh37/hg 19 version. Sanger sequencing was used for evaluation and confirmation of results (Fig. 2A). The primer sequences for the variant to be confirmed were forward 5'-TGTAAAACGACGGCCAGTTTGTGGCAGATAACCCATTCA-3' and reverse 5'-CAGGAAACAGCTATGACCCATTCGCCTGAAGTCAAACAT-3'. We identified that the proband carried a heterozygous frameshift variant c.438_439ins[TCTT; KT192064.1:1_310], p.(Asp147Serfs*33) in exon 5 of *KMT5B* (GenBank: NM_017635.5). This frameshift variant resulted in the insertion of 314 bp in exon 5 of *KMT5B* 438–439. The variant sequence came from *KMT5B* exon 5 434–437 TCTT and AluYa8 (GenBank: KT192064.1) 1–310. The sequence of the inserted 310-bp fragment was as follows: GGCCGGGCGCGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCGAGGCGGGCGGATCACGAGGTCAGGAGATCGA-GACCATCCCGGCTAAAACGGTGAAACCCCGTCTCTACTAAAACTACAAAAAA-TAGCCGGGCGTAGTGGCGGGCGCCTGTAGTCCTAGCTACTTGGGAGGCTGAGGCAGGA-GAATGGCGTGAACCCGGGAGGCGGAGCTTGCAGTGAGCCGAGATCCCGCCACTGCACTCCAGCCTGGGCGACAGAGCGA-GACTCCGTCTCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA. This sequence was derived from the AluYa8 transposon (GenBank: KT192064.1). Sanger sequencing confirmed that his father and younger brother were carriers of the heterozygous variant (Fig. 2B). However, his mother and paternal grandparents were confirmed to not carry the heterozygous variant and had normal clinical manifestation (Fig. 2A). The proband's father also carried a heterozygous variant, but did not manifest an evident clinical phenotype. The proband's younger brother was similar to the proband and was diagnosed with moderate intellectual and developmental disabilities. We will continue to monitor and follow-up with the family members in the future.

3. Bioinformatics analysis

This variant was caused by a 314–bp insertion which were consist of *KMT5B* exon 5 434–437 TCTT and a 310-bp AluYa8 transposon (GenBank: KT192064.1) in exon 5 438–439 positions in the coding region of *KMT5B* (NM_017635.5). It was resulted in a change from asparagine to serine at position 147 and the termination of translation after transcription of 33 amino acids. Comparative amino acid sequence alignment of *KMT5B* across different species at Espript 3.0 (https://espript.ibcp.fr/ESPript/ESPript/) revealed that the asparagine at position 147 is highly conserved [17] (Fig. 2C). To our knowledge, this variant has not been reported or functionally characterized in previous literature and was not found in the searched public databases (ExAC, gnomAD, dbSNP, and 1000 Genomes Project).

This frameshift variant resulted in the insertion of a 314-bp segment in *KMT5B* exon 5 438–439, and the variant sequence came from *KMT5B* exon 5 434–437 TCTT and AluYa8 (GenBank: KT192064.1) 1–310. The variant was inserted in the coding region of *KMT5B* exon located relatively upstream. We utilized the online NMD prediction tool (https://nmdprediction.shinyapps.io/nmdescpredictor/) and found that this frameshift mutation was located in the NMD region. Therefore, we inferred that this variant would ultimately have a potential impact on patients. Moreover, molecular and cellular level experiments were not performed, resulting in insufficient additional evidence to substantiate our findings. Therefore, this type of variant was eventually determined to be likely pathogenic (PVS1+PM2_P) according to the ACMG guidelines. More research is required to verify the ultimate effect of this variant. In the future, we will conduct more studies on this particular variant and enhance monitoring and follow-up with patients to further validate whether this variation will yield subsequent detrimental effects.

To delineate the mutation site and inheritance of *KMT5B* identified in ASD and other NDDs, we summarized missense mutations in histone-lysine N-methyltransferase *KMT5B* (NP_060105.3) (Fig. 3A). Most of the pathogenic variations were because of missense variation, nonsense variation, and splice site variation in the *KMT5B* gene. According to a previous study, haploinsufficiency may be the most likely mechanism of pathogenicity for *KMT5B*, similar to other KMTs and KDMs [18]. Using a combination of human variation databases and existing animal models, *KMT5B* haploid deficiency is closely associated with dominant developmental disorders and leads to overgrowth syndrome with intellectual disability [9,18]. There are three domains in the encoded KMT5B protein: an N domain (pre-SET domain), a SET catalytic domain, and a C domain containing a zinc binding site (post-SET domain). We also predicted the tertiary structure of KMT5B after mutation and compared it with the known DNA binding region of the human SET domain (PDB Code: 5WBV) [11] (Fig. 3B). The novel mutation in this family affected the structure mainly in the α-helix region in the pre-SET domain [11,19,20] (Fig. 3C). Compared with the wild type, the predicting mutant structure lacked in core DNA binding region of SET domain which was known DNA binding region. However, both serine and asparagine at site 147 are neutral amino acids, and no loss was found at the site in multiple species.

4. Discussion and conclusions

KMT5B-related neurodevelopmental disorder is characterized by significantly below-average general intellectual functioning associated with impairments in adaptive behavior and is typically manifested during the developmental period [21]. This autosomal antecedent syndrome was first described in 2014 as caused by mutations in *KMT5B* (NM_017635.5) [5]. To date, *KMT5B*-related neurodevelopmental disorder has demonstrated a variety of clinical phenotypes in patients ranging from 5 to 19 years old. The common phenotypes include developmental delays with mild-to-moderate intellectual disability, poor or absent speech in >75% patients, and motor developmental delays or coordination difficulties in >60% patients. More than 83% children had ASD, and 4 had behavioural abnormalities and attention deficit problems [2,22]. All had additional variable and nonspecific features, including dysmorphic facial features, cryptorchidism, foot deformities, and sleep difficulties, and some had a tendency toward tall stature. Some patients with *KMT5B*-related neurodevelopmental disorder had mild brain abnormalities on MRI, including ventricle enlargement [5,9]. The clinical presentation differed greatly, suggesting the associated *KMT5B* mutation may have disparate pathological effects at the molecular and cellular levels.

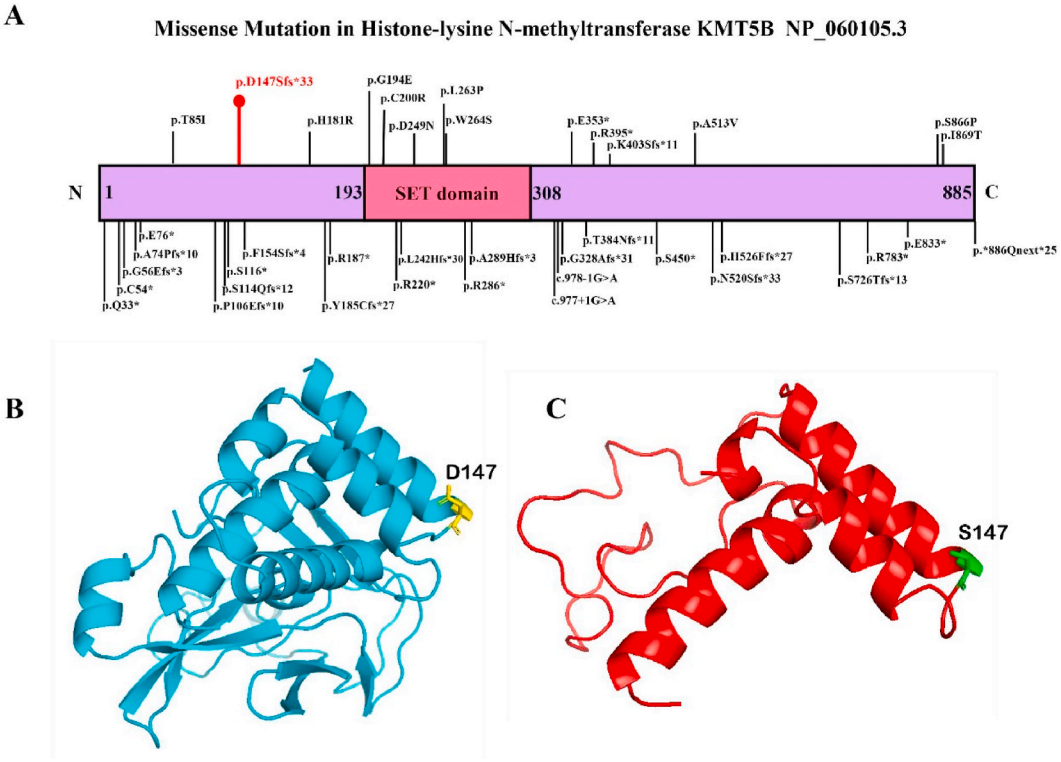

Fig. 3. Schematic diagrams showing structure and variants of KMT5B. (A) The variants were reported in HGMD and the literatures were shown in black, respectively. The position of the variant identified in this study are shown in red. SET domain was the known tertiary structure of the KMT5B (PDB Code: 5WBV). The wide type of the human KMT5B SET domain structure (PDB Code: 5WBV) (B) and the *KMT5B* c.438_439ins[TCTT; KT192064.1:1_310], p.(Asp147Serfs*33) variant on the three-dimensional structure of the protein predicted by functional model software (C). Amino acid was changed from asparagine to serine at position 147, and the overall structure was shortened compared with wild type. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

As the major susceptibility gene, *KMT5B* accounts for more than 80% of all known mutations of *KMT5B*-related neurodevelopmental disorder, as *KMT5B* signaling pathway is crucial for DNA transcription, replication, and damage repair in human development. The inactivation of this pathway is mainly caused *KMT5B*-related neurodevelopmental disorder. *KMT5B* encodes the protein lysine N-methyltransferase 5B, also named SUV420H1, which functions as a protein lysine methyltransferase (PKMT). PKMTs regulate diverse physiological processes including transcription and the maintenance of genomic integrity [11]. Suv4-20 family members are a group of histone H4K20 methyltransferases that play an important role in epigenetic regulation. Mammals have two closely related Suv4-20 paralogs—SUV420H1 and SUV420H2 [19,23]. Genetic studies suggest that SUV420H1 and SUV420H2 facilitate proficient nonhomologous end-joining (NHEJ)-directed DNA repair by catalysing the di- and trimethylation of lysine 20 on histone 4 (H4K20) [11,20,24]. There are many super histone modification pathways that Suv4-20 family members participate in, such as PKMTs methylate histone lysines, chromatin organization, and glucocorticoid receptor regulatory network and so on [25–27]. However, the function of *KMT5B* has not yet been clearly identified, and more work is required to investigate the effect of the de novo variants outside of the SET domain.

In our case report, we presented the details of a Chinese family with the proband, his younger brother, and their father who carried a novel heterozygous frameshift variant in *KMT5B* exon 5 c.438_439ins[TCTT; KT192064.1:1_310], identified by ES. This frameshift variant resulted in the insertion of 314 bp in *KMT5B* exon 5 438–439. The variant was inserted in the coding region of the *KMT5B* exon located relatively upstream. We utilized the online NMD prediction tool (https://nmdprediction.shinyapps.io/nmdescpredictor/) and found that this frameshift mutation was located in the NMD region. Therefore, we inferred that this variant could produce truncated product p.(Asp147Serfs*33) in KMT5B (NP_060105.3), thereby affecting polypeptide chain synthesis and gene function (PVS1). This variant was first observed and not reported in existing databases, including ClinVar, gnomAD, 1000 Genomes Project, ESP, UCSC, ExAC, or dbSNP (PM2_P). The proband and his father and younger brother showed different clinical phenotypes; hence, we could not infer whether co-segregation was affected in this family. We will continue to track and follow-up this family.

In addition, tertiary structure prediction showed that the mutation was located in the α-helix region before the SET domain in SUV420H1, which was highly conserved in multiple species [28,29]. To our knowledge, this kind of mutation is relatively rare in *KMT5B* variations. The proband was diagnosed with *KMT5B*-related neurodevelopmental disorder with neurological abnormalities (developmental delay, mild-to-moderate mental disability, absent speech, and manifestations of ASD) and nonspecific features (macrocephaly, wide eye and nasal bridge, low ear position, social behavior disorder). The father and younger brother showed different clinical manifestations than the proband, suggesting that the *KMT5B* mutation may have different pathologic and physiological effects at the molecular and cellular levels.

Analysis of *KMT5B*-related neurodevelopmental disorder from the available data has shown that all patients had developmental delay with mild-to-moderate intellectual disability, 3 of 4 (75%) had poor or absent speech, and 3 of 5 (60%) had delayed motor development or coordination difficulties. Five of 6 (83%) had ASD, and 4 had behavioural abnormalities, including attention problems. Three patients had a history of febrile seizures. All had additional variable and nonspecific features, including dysmorphic facial features, cryptorchidism, foot deformities, and sleep difficulties, and some had a tendency toward tall stature [2,5]. More than 80% children had recognized ASD. In our study, the proband's parents believe that gene sequencing can help identify major problems of the children's disease and also causing greater psychological burden in the meantime. Therefore, it is necessary to distinguish *KMT5B*-related neurodevelopmental disorder from autism, and next-generation sequencing is a good way to detect these disorders, especially *KMT5B*-related neurodevelopmental disorder. In our case, the proband had non-specific features including macrocephaly, wide eye and nasal bridge, low ear position, and intellectual disability with absent speech. On the one hand, our new finding not only broadens the mutation spectrum of *KMT5B* but also provides supportive genetic counselling regarding reproductive choices. On the other hand, it is necessary for parents and clinical medical staff to carry out systematic physical examinations for children with special facial features or autistic behavior, including genetics testing and etiological analysis.

In conclusion, we present the clinical details of a Chinese family with *KMT5B*-related neurodevelopmental disorder who carried a novel heterozygous variant in *KMT5B*. The report broadened genetic spectrum of the *KMT5B* mutations were related to *KMT5B*-related neurodevelopmental disorder. This study may aid in diagnosis, carrier detection, and genetic counselling of *KMT5B*-related neurodevelopmental disorder.

5. Limitation

Our reported study did not include functional studies of this newly identified variant to determine its specific pathogenic effect on *KMT5B* gene function. Future research will be targeted toward identifying the contribution of this variant, but also to elucidate how such a point mutation gives rise to various phenotypes. Another technical limitation was that we have not determined whether other family members of the proband carry this variant. We also did not use medical methods to assess the intelligence of father. We will continue to follow the clinical outcomes of the family.

Data availability statement

The datasets for this article are not publicly available due to concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding author.

Ethical compliance

The proband's parents provided written informed consent to participate in this study in compliance with the Declaration of Helsinki, and the Institutional Review Board at Lianyungang Maternal and Child Health Hospital approved this study (Project no. LW2023003).

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CRediT authorship contribution statement

Jiao Tong: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Xu Chen:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Xin Wang:** Investigation, Data curation. **Shuai Men:** Methodology, Investigation, Formal analysis. **Yuan Liu:** Methodology, Investigation, Formal analysis. **Xun Sun:** Investigation, Data curation. **Dongmei Yan:** Writing – review & editing, Conceptualization. **Leilei Wang:** Writing – review & editing, Data curation, Conceptualization.

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.

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List of abbreviations

OMIM	Online Mendelian Inheritance in Man
ES	Exome Sequencing
ID	Intellectual Disability
HGMD	Human Gene Mutation Database
MRI	Magnetic Resonance Imaging
EEG	Electroencephalography
ABC	Autistic Behavior Checklist
CARS	Childhood Autism Rating Scale
ACMG	American College of Medical Genetics and Genomics
KMT5B	Lysine N-Methyltransferase 5B
SUV420H1	Su(Var)4–20 Homolog1
H4K20	Lysine 20 on histone 4
KMTs	Histone lysine methyltransferases
KDMs	Histone lysine demethylases
RMTs	Arginine methyltransferases
SAM	S-adenosyl-L-methionine.

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