

Wiedemann-Steiner Syndrome Caused by Novel Mutation of KMT2A Gene: A Report of Two Cases

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ABSTRACT Wiedemann-Steiner Syndrome (WDSTS, OMIM 605130) is a rare autosomal dominant disorder. This case report describes two related cases and explores new mutation sites, aiming to provide new reference cases for clinical use. This report presents two female pediatric cases characterised by hirsutism, facial deformities, and intellectual disabilities, investigated via molecular genetic analysis. Patient 1 showed precocious puberty, hirsutism, facial deformities, congenital heart disease, astigmatism, pilonidal sinus, growth retardation, and intellectual disability. Patient 2 exhibited severe growth and developmental delays, astigmatism, facial deformities, and hirsutism. Whole-exome sequencing identified a KMT2A:c.666delA (p.Gly223Glufs*9) variant in Patient 1 and KMT2A:c.5664+1G>C in Patient 2. Patient 1 received gonadotropin-releasing hormone analogs for puberty control and growth hormone therapy, resulting in improved growth and metabolic rates. These findings expand the KMT2A mutation spectrum and highlight the value of genetic testing for children with growth retardation, hirsutism, and intellectual disabilities.

INTRODUCTION

Wiedemann-Steiner syndrome (WDSTS; OMIM 605130) is a rare autosomal dominant genetic disorder caused by heterozygous pathogenic variants in the KMT2A gene (previously known as the MLL gene, located at 11q23.3). This condition was initially reported by Wiedemann and Steiner in 1989 and 2000, respectively (Stellacci et al. 2016). Its molecular mechanism was first identified as being associated with mutations in the KMT2A gene by Jones et al. in 2012 (Baer et al. 2018; Enokizono et al. 2020). KMT2A encodes a histone methyltransferase that plays a role in early development and neural differentiation by regulating chromatin-mediated transcription (Giangiobbe et al. 2020; di Bari et al. 2024). Dysfunction of this gene can lead to multisystem developmental disorders. The core clinical features of WDSTS include growth retardation, intellectual disability/developmental delay, distinctive facial characteristics (such as broad nasal bridge, thick eyebrows, and long eyelashes), and hypertrichosis, typically manifesting as hairy elbows (Luo et al. 2021; Demir et al. 2021; Wang et al. 2023). However, the phenotypic heterogeneity is significant, with some patients lacking typical hairy elbows or presenting only with mild neurodevelopmental abnormalities, adding complexity to clinical diagnosis (Foroutan et al. 2022; Jinxiu et al. 2020).

In recent years, the application of high-throughput sequencing technology has significantly improved the molecular diagnostic rate of WDSTS. Currently reported variations in the KMT2A gene include nonsense mutations, frameshift mutations, and splice site variations (Sheppard et al. 2021; Carman et al. 2020; di Bari et al. 2024; Nishimura et al. 2025). These variations lead to abnormal histone modifications through a haploinsufficiency mechanism, thereby affecting downstream gene expression, particularly in signalling pathways related to neural development (di Bari et al. 2024). It is worth noting that the incidence of growth retardation in WDSTS patients is over 80 percent, which may be associated with abnormalities in growth hormone secretion or signalling pathways. Growth hormone therapy has shown potential for improving linear growth in some patients (Lin et al. 2023). Additionally, there has been a gradual increase in reports of atypical phenotypes such as precocious puberty and congenital heart disease, indicating a need for broader clinical recognition of the phenotypic spectrum of this syndrome (Wang et al. 2023). The researchers report two cases of children presenting with hypertrichosis, facial deformities, and intellectual disability. Among them, one case primarily manifested as central precocious puberty, which is relatively rare in previous reports of WDSTS.

Additionally, both patients exhibited novel variations in the KMT2A gene, which can assist clinicians in enhancing their understanding of this disease.

Objectives

This study reports the clinical characteristics of two cases of WDSTS in China and identifies the underlying causes and KMT2A mutation sites through molecular genetic analysis, with the aim of providing a clinical reference.

METHODOLOGY

Clinical Information

Data collection was conducted in December 2024. Clinical data were obtained for two female pediatric patients, whose manifestations included hirsutism, facial dysmorphism, and intellectual disability. A comprehensive clinical evaluation was performed by reviewing medical records and conducting detailed assessments, including physical examination (height, weight, facial features, hair distribution, and genital development), ancillary investigations (chromosomal analysis, bone age assessment, breast, uterine, and ovarian ultrasonography, hormone level testing, and growth hormone stimulation test), and developmental evaluation.

Genetic Analysis and Variant Annotation

Peripheral venous blood (3-5 ml) was collected from patients and their parents. Genomic DNA was extracted, and exonic regions (coding sequences of ~20,000 genes) were enriched using targeted capture kits. Sequencing was performed on a high-throughput platform (for example, Illumina NovaSeq) to generate paired-end reads.

Core Questions

The study aimed to answer the following research questions:

1. What is the genetic etiology underlying the clinical phenotypes of these two pediatric patients?
2. Can genetic testing identify novel KMT2A variants to expand the mutation spectrum of WDSTS?
3. Is combined treatment with GnRHa and growth hormone effective for WDSTS patients with precocious puberty and growth retardation?

Case 1

A 7-year-old female patient presented to the Women and Children's Hospital Affiliated to Ningbo University in June 2020 due to "repeated breast lumps for more than 2 years". She was the first child of her parents, born via full-term cesarean section. Her birth weight was 2.75kg, and there was no history of asphyxia, cyanosis, or resuscitation. Her language and motor development were delayed compared to normal peers. The patient underwent surgical treatment for "patent ductus arteriosus and pulmonary hypertension" at 42 days of age. She also had congenital astigmatism. Sensory integration examination revealed severe dysfunction of vestibular balance and bilateral brain differentiation, as well as mild developmental motor dysfunction. Both parents were healthy and had no history of early development.

Her height was 118.4 cm, with a body weight of 18.5 kg. She exhibited longer and denser hair on her limbs and back, as well as thick hair and eyebrows (Fig. 1A-1C). Her nasal bridge was low and flat, and her nose tip was broad (Fig. 1A-1C). Her thoracic cage appeared asymmetric, and there was an 8 cm scar under her left scapula. Her breasts were in stage B2, measuring 1.5×1.5 cm, with dark areolas and prominent nipples. Her external genitalia were of the infantile type, with no visible pubic hair, a PH of 1, and a slightly enlarged clitoris. A pilonidal sinus was visible in the lumbosacral region (Fig. 1D). Chromosome analysis revealed a 46, XX karyotype. Bone age examination indicated an age of approximately 8 years and 10 months. Breast ultrasonography showed echoes of glandular tissue behind both left and right nipples, with the thickest parts measuring 5.7 and 5.9 mm respectively, indicating the presence of glandular tissue in both breasts. Transabdominal ultrasonography of the uterus and adnexa revealed a uterus size of approximately 22×6×13 mm, a left ova-



Fig. 1. Facial and Hypertrichotic Features of Case 1 with Wiedemann-Steiner Syndrome

(A) Facial characteristics: dense hair, thick eyebrows, long eyelashes, flat nasal bridge, and broad nasal tip

(B) Hypertrichosis on the back

(C) Hypertrichosis on the elbows

(D) Sacrococcygeal pilonidal sinus

ry size of 27×12×14 mm, and a right ovary size of 28×13×14 mm. Numerous follicles were visible within the ovaries, with the largest measuring 6 mm in diameter. The LHRH stimulation test indicated an LH peak of 10.75 mIU/mL. The ratio of LH peak to FSH peak was approximately 0.6, suggesting central precocious puberty.

Peripheral venous blood (3–5 ml) was collected from the proband and her parents for

whole-exome sequencing and Sanger sequencing. The results indicated a heterozygous variant c.666delA (p.Gly223Glufs*9) in the KMT2A gene of the patient, which was located in exon 11 and is a truncation variant (Fig. 2). According to the ACMG guidelines, this variant was classified as pathogenic (PVS1+PM2+PP4). The evidence is that PVS1 refers to the situation where the detected variant is a null variant (nonsense,

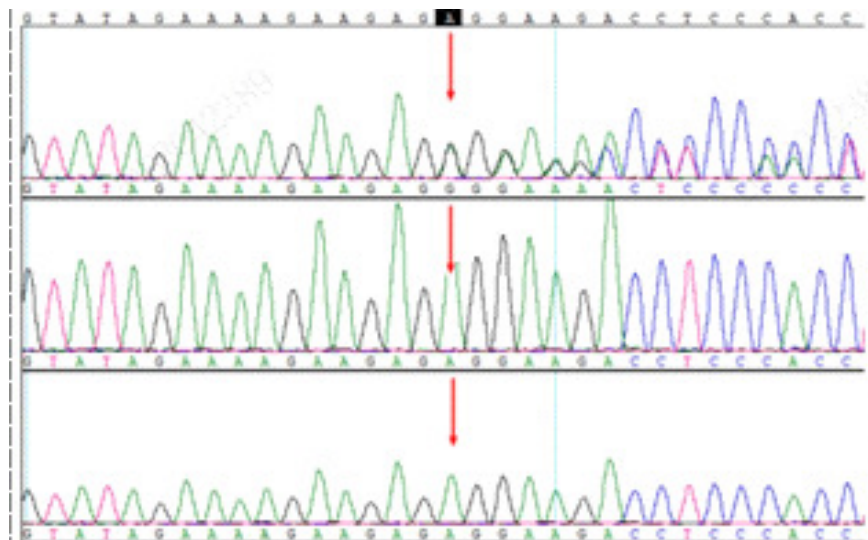


Fig. 2. Case 1 harbours a c.666delA variant in the KMT2A gene, which was not detected in either parent

frameshift, canonical ± 1 or 2 splice site, initiation codon, single or multiexon deletion) in a gene where loss of function (LOF) is a known mechanism of disease. PM2 indicates that the variant is absent from controls (or at extremely low frequency if recessive) in the ESP, 1000 Genomes, or EXAC databases. PP4 signifies that the phenotype of the variant carrier, or the family history, is highly specific for a single gene disorder. Neither of her parents carried this variant, suggesting that it is a *de novo* mutation.

The child was treated with GnRHa (3.75 mg per injection, administered every 28 days) for central precocious puberty. After 6 months of treatment, the child was 7 years and 7 months old, with a height of 122 cm, and the bilateral breast masses had resolved. The bone age was reassessed as 8.5 years. The reproductive hormone levels included LH of 1.35 mIU/mL, FSH of 1.39 mIU/mL, and E² of <20 pg/mL, which had returned to pre-pubertal levels. After 8 months of GnRHa therapy, the child was also started on growth hormone treatment. At the time of the study, the child was 9 years and 5 months old, with a height of 141 cm and a weight of 31 kg. The breasts were at stage B1. The reproductive hormone levels included LH of 1.01 mIU/mL, FSH of 4.19 mIU/mL, and E² of <15 pg/mL. The last injection of GnRHa was administered in June 2024, and GH treatment was stopped in September 2024.

Recent follow-up showed that the child was 11 years and 5 months old, with a height of 154.5 cm and a weight of 39.0 kg. The breasts were at stage B3, with no significant pigmentation of the areola. Pubic hair was at stage PH2, and the external genitalia appeared juvenile. There were no visible deformities of the spine.

Case 2

The patient, a 4-year and 6-month-old female child, presented to Women and Children's Hospital Affiliated to Ningbo University in August 2021 due to "slowed growth rate for more than 3 years". The child's growth rate began to slow down more than 3 years ago, with only 3 cm of growth in the past year. The mother of the child experienced a miscarriage during her first trimester of her first pregnancy and a biochemical pregnancy for her second. This child, the third pregnancy and third birth (G3P3), was born at 35

weeks via normal delivery due to "premature rupture of membranes", with a birth weight of 2.66 kg. The child's language and motor development lagged behind peers. Since birth, the child has suffered from frequent respiratory infections and was diagnosed with congenital astigmatism and strabismus. Both parents are healthy and did not experience precocious development.

Physical examination revealed a weight of 14 kg and a height of 97.2 cm. The child has a round face, bulbous nose, and a low, flat nose bridge (Fig. 3A). The child has long and dense body hair on the limbs and back. The breasts are at stage B1 of development Fig. 3B-3D. The external genitalia appear normal, with no pubic hair visible, indicating stage PH1. The bone age was equivalent to that of a 3-year and 6-month-old child. The insulin-like growth factor-1 level was 74.1 ng/mL, and the Insulin-like growth factor-binding protein-3 was 3.29 ng/mL. The growth hormone stimulation test showed a peak GH value of 4.25 ng/mL, suggesting a complete deficiency of growth hormone.

The results of whole-exome sequencing revealed a heterozygous canonical splicing variant in the KMT2A gene: c.5664+1G>C (Fig. 4). This variant represents a single-base substitution in the splicing region of the KMT2A gene, which may cause abnormal splicing of the KMT2A gene or nonsense-mediated mRNA decay. Sanger sequencing confirmed that this variant was not present in the parents of the patient, indicating that it is a *de novo* variant. According to the ACMG guidelines, this variant is classified as a likely pathogenic variant (PVS1+PM2_Supporting). The evidence is that for PVS1, the ClinGen database categorises KMT2A gene haploinsufficiency into three classes, with the corresponding phenotype being Wiedemann-Steiner syndrome. This suggests that the pathogenic mechanism of the KMT2A gene is loss of function. The variant is a classic splicing variant, which may lead to loss of gene function. PM2_Supporting, wherein this variant is rare and is not recorded in the gnomAD database.

The patient exhibited a significant lack of growth hormone. Following the exclusion of any contraindications for its use, growth hormone treatment was intended to enhance her stature. However, due to her parents' financial difficulties, she has not yet received growth hormone treatment.



Fig. 3. Facial and hypertrichotic features of Case 2 with Wiedmann-Steiner Syndrome
 (A) Facial characteristics: dense hair, thick eyebrows, long eyelashes, and bulbous nose
 (B) Hypertrichosis on the back
 (C) Hypertrichosis on the elbows
 (D) Hypertrichosis on the legs

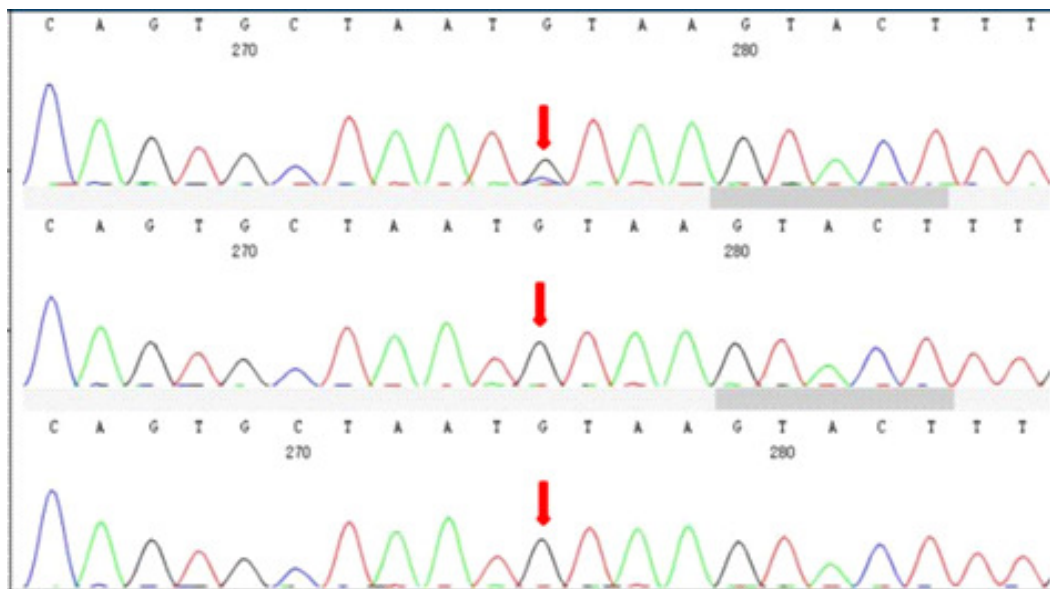


Fig. 4. Case 2 harbours a c.5664+1G>C variant in the KMT2A gene, which was not detected in either parent

RESULTS AND DISCUSSION

WDSTS is an exceedingly rare autosomal dominant genetic disorder affecting growth and development, with a global incidence rate of less than 1/1,000,000. The clinical manifestations are

diverse, most commonly including hirsutism, delayed growth and development, intellectual disability, and distinctive facial features. With the advancement of whole-exome sequencing, the phenotypic spectrum of WDSTS has continued to expand (Di Fede et al. 2021), and novel

variants in the KMT2A gene have steadily increased. So far, over 200 KMT2A gene variations have been reported in the human gene variation database, with missense, nonsense, and frameshift mutations being the most prevalent. The KMT2A gene, located at 11q23.3, spans 87 kb and comprises 36 exons. It encodes the transcriptional coactivator lysine methyltransferase 2A, a protein consisting of 3,969 amino acids with eight conserved functional domains from the 3' N-terminus to the 5' C-terminus. KMT2A encodes a DNA-binding protein that methylates histone H3 at lysine 4 (H3K4), modifying chromatin structure and upregulating HOX and WNT genes (Jinxu et al. 2020).

In a recent large-sample cohort study involving 104 individuals, the common clinical features of Wiedemann-Steiner Syndrome were identified as developmental delay or intellectual disability (97%), constipation (63.8%), hypoplasia (67.7%), feeding difficulties (66.3%), hypertrichosis of the elbows (57%), short stature (57.8%), and spinal abnormalities (46.9%) (Sheppard et al. 2021). Compared to a previous meta-analysis (Chan et al. 2019), this study found a higher proportion of neurological abnormalities among the patients. In this cohort of 104 patients, Pearson's chi-square test was applied to determine the genotype-phenotype correlation between patients with KMT2A LoF variants (n=64) and those with other variants (n=18). The study revealed that patients with LoF variants were more prone to develop hypotonia, whereas patients with non-LoF variants were more likely to experience epileptic seizures. This suggests an association between hypotonia and loss-of-function (LoF) variants, and between epileptic seizures and non-LoF variants, providing some clarity on the genotype-phenotype correlation (Chan et al. 2019). In a French case study involving 33 WWS patients, 4 cases of epileptic seizures were reported, with 3 of them exhibiting missense variants in the CXXC DNA domain. This implies that defects in this domain may lead to abnormal neurological development, resulting in brain dysfunction manifesting as intellectual disability, sensory integration dysfunction, hyperactivity disorder, epilepsy, etc. (Baer et al. 2018). Changes in endothelial nitric oxide and the WNT pathway caused by KMT2A may be associated with cognitive dysfunction (Mietton et al. 2018).

Meanwhile, studies have shown that data obtained from knockout mice and zebrafish embryos demonstrate the critical role of KMT2A in the proliferation of neural precursor cells, differentiation of neurons and glial cells, and synaptic plasticity (Jakovcevski et al. 2015).

In this study, variations in the KMT2A gene were detected in both patients, leading to a diagnosis of WDSTS. Both cases presented with growth impairment, developmental delay, and craniofacial anomalies, including dense hair and eyebrows, downslanting palpebral fissures, ptosis, ocular malformations (strabismus, hyperopia, and astigmatism), a round and broad nasal tip, and hypertrichosis, most prominently observed on the elbows. Central precocious puberty was observed in Case 1, which is a rare finding in previously reported cases of WDSTS. The primary reason for Case 2's clinic visit was significant height retardation, suggesting that a thorough understanding of developmental history, coupled with detailed physical examination and developmental assessment, can aid in the early identification of WWSTS in children presenting with growth retardation and prominent hypertrichosis. Both patients exhibited marked hypertrichosis, and studies have demonstrated that variations in the KMT2A gene can affect signalling pathways involved in stimulating hair growth, such as the eNOS (cell proliferation) and BMP pathways. Dysregulation of these pathways can lead to systemic vasodilation, increasing blood circulation to hair follicles and bulbs, thereby promoting hair growth (Mietton et al. 2018).

Additionally, a case report described a patient without clinical manifestations of hypertrichosis who was initially diagnosed with blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) based on ocular symptoms, but later genetically confirmed as WDSTS. This indicates that not all patients present with hypertrichosis (Jinxu et al. 2020). A study in China involving 16 confirmed cases identified six novel clinical phenotypes, including microcephaly, deep palmar creases, external ear malformations, delayed growth of carpal epiphyses, dyslipidemia, and decreased skin gloss (Li et al. 2018). Manav et al. (2025) investigated patients with Wiedemann-Steiner syndrome (WDSTS) in a Turkish population and examined their clinical and genetic characteristics. Among the 16 pa-

tients included in the study, 15 KMT2A mutation sites were identified in exons, leading to alterations in the protein sequence, while one was located in an intron. All patients exhibited varying degrees of neurological impairment, predominantly developmental and speech delays. The current study further highlights the occurrence of central precocious puberty among female patients. However, the presence of central precocious puberty in Case 1 raises the question of whether this expands the clinical phenotypes of the disease, which requires further confirmation and support from additional clinical vignettes.

Due to the phenotypic manifestations of WDSTS, which include short stature, hirsutism, long eyelashes, and prominent eyebrows, it is necessary to differentiate it from other syndromes with overlapping clinical phenotypes. These include Kabuki syndrome, Cornelia de Lange syndrome, Rubinstein-Taybi syndrome, Floating-Harbor syndrome, and Coffin-Siris syndrome. Kabuki syndrome is characterised by a distinct facial appearance with long eyelids, ectropion of the lateral eyelids, arched eyebrows, sparsity of the outer 1/3 of the eyebrows, and long and slender eyelashes. Abnormal skin patterns are common, accompanied by intellectual disability, growth retardation, and other congenital abnormalities. Abnormalities in the KMT2D gene and the KDM6A gene are the main genetic causes of Kabuki syndrome type I and type II, respectively (Miyake et al. 2016). Cornelia de Lange syndrome is primarily recognised by its distinct facial features, including synophrys and arched eyebrows, long eyelashes, a long and prominent philtrum, and a small or square-shaped jaw. Limb defects are often present, and the pathogenic genes include NIPBL, SMC1A, SMC3, RAD21, and HDAC8 (Yuan et al. 2015). Rubinstein-Taybi syndrome presents with characteristic developmental abnormalities, including a distinct facial appearance (high eyebrow arches, long eyelashes, high palatal arches, and an unusual smile), growth and developmental delay, structural malformations (such as broad and flat thumbs or toes), and intellectual disability. Variations in the CREBBP and EP300 genes can confirm the diagnosis (Di Fede et al. 2021). Floating-Harbor syndrome is clinically characterised by short stature, delayed bone age, de-

layed language development, abnormal facial features, intellectual disability, and, in some cases, behavioural abnormalities. The SRCAP gene is the main pathogenic gene (Budisteanu et al. 2018). Coffin-Siris syndrome is a rare congenital genetic syndrome associated with multiple system disorders, including congenital abnormalities, malformation features, recurrent infections, and developmental delay. Typical features include hypoplasia of the distal phalanges or fifth fingers/toes, distinct facial features (bushy eyebrows, broad nasal bridge, wide mouth, hirsutism), microcephaly, organ dysfunction, and varying degrees of developmental or cognitive impairment. It is caused by mutations in genes encoding the human BRG1-associated factor (BAF) chromatin-remodelling complex, also known as the SWI/SNF-A complex. SWI/SNF gene mutations mainly concentrate in the catalytic and regulatory subunits, primarily involving genes such as ARID1A, ARID1B, SMARCA4, SMARCB1, SMARCE1, and SOX11 (Negri et al. 2019). Therefore, relying solely on clinical manifestations can sometimes be challenging for differential diagnosis, and genetic testing of suspicious cases can provide a definitive diagnosis.

Currently, there is no specific treatment for this disease, and all treatments are symptomatic. Patients with psychomotor retardation and decreased muscle tone require language or motor rehabilitation training. According to literature reports, 50 percent (6 out of 12 cases) of patients suffer from growth hormone deficiency. However, whether growth hormone levels are normal or reduced, the administration of growth hormone therapy to patients with short stature has achieved good results (Baer et al. 2018). Stoyale et al. (2018) reported the long-term efficacy of a six-year rhGH monotherapy in a child with WDSTS. The child's height increased by 3.1 SDS, and no adverse reactions were observed. In this study, Case 1 received GnRHa to control precocious puberty while simultaneously receiving growth hormone therapy to improve height and cognitive function. After 19 months of growth hormone therapy, the patient's height increased by 18 cm. Currently, there have been no reported cases of tumour development after growth hormone therapy, but regular monitoring of blood routine, mediastinal ultrasonography, and long-term follow-up studies with large

samples are needed to assess the risks (Baer et al. 2018). Ophthalmic surgery can be performed to correct ptosis, small palpebral fissure, strabismus, and lacrimal duct abnormalities. Refractive errors can be corrected by wearing glasses after a complete refractive examination. In this study, two children had congenital astigmatism and were treated with corrective eyewear. Surgical treatment can be given for combined heart malformations. Patients with epileptic seizures can be treated with anti-epileptic drugs.

Yuill et al. (2025) conducted in-depth interviews with parents of children diagnosed with WDSTS in the United Kingdom and the United States. Four major themes emerged for intense sociability, interpersonal and executive dysregulation, sensory sensitivity, and cognitive patterns characterised by uneven memory and poor comprehension. This study underscores the significance of psychological interventions for affected children. However, this aspect is not adequately addressed in the current findings, prompting the need to implement a psychosocial health care strategy for rare cases integrated with symptomatic disease management.

CONCLUSION

In conclusion, children presenting with growth retardation accompanied by mental retardation, distinct facial features, and hirsutism should be considered for WDSTS. The etiology can be determined based on biological, genetic, and clinical factors. GnRHa combined with rhGH effectively controlled sexual development while improving the patient's final adult height.

RECOMMENDATIONS

Children with growth retardation, hirsutism, distinctive facial features, and intellectual or developmental delays should be prioritised for WDSTS evaluation, with timely genetic testing to confirm KMT2A variants. Comprehensive assessment is essential to detect complications such as precocious puberty or congenital anomalies. Targeted therapy, GnRHa for precocious puberty and growth hormone for growth retardation, along with multidisciplinary management and long-term follow-up, is recommended to improve outcomes.

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