Letter to the editor

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Growth hormone deficiency in a boy with Wiedemann-Steiner syndrome: a case report and review

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Highlights

- A Korean pediatric case of Wiedemann-Steiner syndrome (WSS) highlights a *de novo* *KMT2A* gene variant, presenting with facial dysmorphism and developmental delay. The patient, diagnosed with growth hormone deficiency (GHD), showed significant height improvement with recombinant human growth hormone treatment, emphasizing the need to consider WSS in GHD cases.

To the editor,

Wiedemann-Steiner syndrome (WSS) is a rare, autosomal dominant genetic disorder caused by mutations in the lysine (K)-specific methyltransferase 2A (*KMT2A*) gene.[1,2] It is characterized by a broad phenotypic spectrum, including facial dysmorphism, hypertrichosis, short stature, and developmental delay.[1,2] It was recently reported that growth hormone deficiency (GHD) might also be found in patients with WSS[3,4] Herein, we report a case of WSS in a boy who also had GHD.

A 2-year-old boy born to nonconsanguineous Korean parents presented with short stature and developmental delay. He was born at 39^{+2} weeks of gestational age with a birth weight of 3,595 g (50th–75th percentile), length of 50.5 cm (50th–75th percentile), and head circumference of 36.5 cm (90th–95th percentile). Polyhydramnios was apparent in the prenatal period, with no other specific perinatal or family history. His delivery was normal, with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. Neonatal screening tests, including tandem mass, were all normal. At 9 months of age, axial hypotonia and developmental delay were suspected. He was able to walk independently at 18 months of age. At 24 months of age, the BSID-II (Bayley Scales of Infant Development II) showed a global developmental delay. An examination revealed hypermetropia, strabismus, high-arched palate, open mouth, torticollis, and simian lines. Genetic studies, including multiplex ligation-dependent probe amplification, ruled out congenital myotonic dystrophy and other related disorders.

His growth velocity decreased gradually after 18 months. At 24 months, his height was 81.1 cm (below the 3rd percentile), weight was 10.5 kg (10th percentile), and head circumference was 48.6 cm (50th–75th percentile). His mean parental height was 173.5 cm (25th–50th percentile). His thyroid function (TSH 1.95 uIU/ml and FT4 1.54 ng/dL) was normal. The insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 levels were 32.4 ng/mL (10th–25th percentile) and 1,970 ng/mL (50th–75th percentile), respectively. The patient was diagnosed with GHD through a growth hormone (GH) provocation test (peak GH level was 6.9 ng/mL). Magnetic resonance imaging of the brain showed normal findings.

Because of the patient's dysmorphic features and developmental delay, whole-exome sequencing was performed and identified a de novo heterozygous variant of *KMT2A*:c.731T>G(p.Leu244*. This variant, which is located within exon 3 of the *KMT2A* gene on chromosome 11, was confirmed by targeted Sanger sequencing (Fig. 1). The variant creates a stop codon at codon 244, resulting in premature termination of the protein product and was classified as likely pathogenic according to the recommendations of the American College of Medical Genetics (ACMG) guidelines.[5] This novel variant was added to the Clinvar database (SCV002012176.1).

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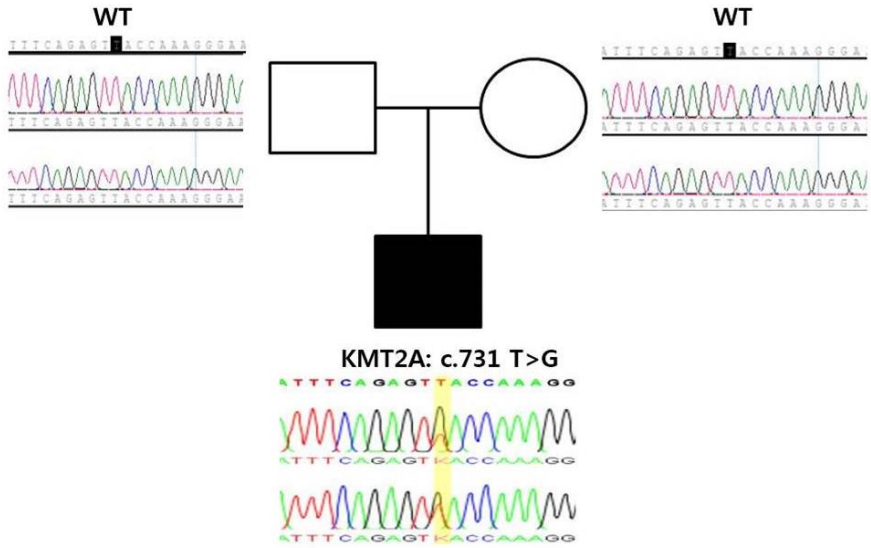

Fig. 1. Family tree and chromatograms of the causative genetic mutation in the patient and parents. The blank square and circle indicate the unaffected father and mother, respectively; the filled square indicates the affected patient. Sanger sequencing confirmed a c.731T>G (p.Leu244*) mutation in the *KMT2A* gene of the patient. However, the parents did not have a mutation in the *KMT2A* gene. WT, wild type.

Recombinant human GH treatment was started with an initial dose of 0.1 IU/kg/day, which resulted in a significant improvement in height. The child's height increased to the 10th percentile after 1 year.

To date, more than 50 studies of WSS have been reported. According to the Leiden Open Variation Database (2022/03/28), 281 public variants have been reported. The Clinvar database lists 137 variants, with 102 classified as pathogenic or likely pathogenic (2022/03/24). In addition, 35 variants are identified as nonsense mutations, 50 as missense mutations, 41 as frameshift mutations, and 10 as splicing mutations. The characteristics and pathogenic variants of patients with WSS reported in the literature are presented in Table 1.

KMT2A, located on chromosome 11q23.3, contains 36 exons; however, most mutations are on exon 27, with one on exon 3.[2] The *KMT2A* gene encodes a histone 3 lysine 4 methyltransferase, which is critical for DNA packing, chromatin modification, and gene expression regulation as an epigenetic writer. As *KMT2A* is widely expressed in almost all tissues, the phenotypes of patients with WSS involve multiple body systems, including facial features, skeletal anomalies, and developmental disability.[6]

Recent studies have suggested a link between WSS and GHD, although the underlying mechanism remains unclear.[3,4] GHD has also been observed in other syndromes that involve the *KMT2* gene family, such as Kabuki syndrome and CHARGE, which indicates a potential role in the hypothalamic pituitary axis.[7,8]

In conclusion, this report details the first case of WSS in a Korean pediatric patient with accompanying GHD. Our case emphasizes the importance of considering WSS in children with GHD who present with other clinical features such as facial dysmorphism and developmental delay. This case also contributes valuable insights to the understanding of the phenotypic spectrum of WSS and its association with GHD.

Notes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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Ethics statement: Written informed consent for publication of this case report was obtained from the patient's parents.

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Table 1. Summary of phenotypes and genotypes in patients with Wiedemann-Steiner syndrome reported in the literature

No.	Study	Age/ sex	Dysmorphism	Accompanying anomalies	Intellectual disability or neurologic finding	Endocrine dysfunction or GHD	The mutation in the *KMT2A* gene
1	Hirst and Evans[9] (2021), UK	7 Years/ female	Telecanthus, flared medial eyebrows, long and narrow palpebral fissures, long philtrum, bilateral ear pits, premature exfoliation of primary teeth, premature eruption of permanent teeth, hypertrichosis	Bilateral hip dysplasia, sacral dimple	Intellectual disability	AGA	c.3082A>T(p.Lys1028Ter)
2	Ramirez-Montano et al.[6] (2019), Southwest Colombia	21 Months/ female	Low anterior hairline, thick hair, synophrys, hypertelorism, long eyelashes, downslanted palpebral fissures, ptosis, Dennis Morgan folds, epicanthic folds, low-set ears, wide and depressed nasal bridge, long philtrus, hypertrichosis	Bilateral hip dislocation	Intellectual disability, hypotonia	AGA, short stature (-3.83 SDS)	c.4177dupA(p.Ile1393Asnfs*14), exon 9
3	Stoyle et al.[3] (2018), UK	8.6 Years/ male	Facial asymmetry, thick arched eyebrows, long eyelashes, downslanting and narrow palpebral fissures, ptosis, hypertelorism, low-set ears	Vesicoureteric reflux, hydronephrosis, hydroureter	Intellectual disability, anterior pituitary hypoplasia with ectopic posterior pituitary	AGA, short stature (-4.5 SDS), GHD	c.7062delC(p.Ser2355LeufsTer18)
4	Aggarwal et al.[2] (2017), USA	5 Years/ male	Thick eyebrows, downslanting and narrow palpebral fissures, long eyelashes, epicantal folds, ptosis, widely spaced eyes, strabismus, low-set ears, broad nose, long philtrum, thin upper lip, downturned corners of mouth, hirsutism	Unilateral mild left hydronephrosis, mild right pelviectasis	Mild intellectual disability	SGA, short stature (-3.8 SDS)	c.152_186del(p.Pro51Argfs*84), exon 1
5	Ko et al.[10] (2017), Korea	4.2 Years/ female	Thick eyebrows and hair, short palpebral fissures, ptosis, hypertelorism, low-set ears, wide and depressed nasal bridge, short nose, bulbous nose, hypertrichosis	Congenital muscular torticollis, patent ductus arteriosus, developmental dysplaia of hip, clinodactyly	Borderline intellectual disability (IQ 70)	SGA, short stature (-3.0 SDS)	c.5932C>T(p.Gln1978*)
6	Ko et al.[10] (2017), Korea	8 Years/ male	Thick or arched eyebrows with lateral flare, downslanting palpebral fissures, hypertelorism, low-set ears, wide and depressed nasal bridge, bulbous and short nose, simian line, hypertrichosis,	Clinodactyly	Severe intellectual disability (IQ<30), hypotonia	AGA	c.3504G>A(p.Gly1168Asp)

WSS, Wiedemann-Steiner syndrome; GHD, growth hormone deficiency; AGA, appropriate for gestational age; SGA, small for gestational age; SDS, standard deviation socore; IQ, intelligence quotient.

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