CASE REPORT

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Clinical and Molecular Landscape of Weiss-Kruszka Syndrome: A Case Report and Literature Review

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What is already known on this topic?

Weiss-Kruszka syndrome (WSKA; OMIM#618619) is a rare condition with multiple congenital anomalies. The syndrome is linked to a heterozygous pathogenic variant in the zinc finger protein 462 gene (*ZNF462*, MIM#617371) and deletion of the 9q31.2 chromosome region involving *ZNF462*.

What this study adds?

This study describes a patient with WSKA from Northern China caused by a novel *de novo* splicing variant in the *ZNF462* gene. We also review and analyze reported cases to describe the clinical and molecular landscape of WSKA and improve clinical diagnosis and management of this rare syndrome.

ABSTRACT

Weiss-Kruszka syndrome (WSKA; OMIM#618619) is a rare condition with multiple congenital anomalies. This study describes a patient with WSKA from Northern China. The patient was a 9.75-year-old boy who presented with growth retardation (growth velocity: 3-4 cm/year at school age), delayed motor and speech development, and eating difficulty. The patient's weight was 22 kg (<3rd percentile), and his height was 125.6 cm (<3rd percentile) at the first visit. He had craniofacial anomalies characterized by heavily arched eyebrows, mild bilateral ptosis, inner epicanthal folds, uneven teeth, macrodontia of the upper central incisors, and low-set ears. A transverse palmar crease was observed on the right palm. The serum insulin-like growth factor-1 level was 73.1 ng/mL (normal range: 74-388 ng/mL). His bone age was appropriate at 9-10 years. Cranial magnetic resonance imaging results revealed a small pituitary gland. Trio whole-exome sequencing was performed because of the patient's non-specific dysmorphic features and a phenotype indistinguishable from many other inherited disorders with growth retardation.

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A *de novo* splicing variant, c.6833-2A>T, was identified in the *ZNF462* gene (NM_021224). Recombinant human growth hormone therapy was started (dose, 0.15 IU/kg/day) and administered as daily subcutaneous injections. His growth velocity increased (5 cm/6 months). This case has been added to the limited number of publications reporting WSKA. This study also reports the genotypic and phenotypic landscape of WKSA, providing clinical and genetic data to support the etiology of haploinsufficiency of the *ZNF462* gene, as postulated by previous studies.

Keywords: *ZNF462* gene, genotypic, phenotypic, Weiss-Kruszka syndrome

Introduction

Weiss-Kruszka syndrome (WSKA; OMIM#618619) is a rare genetic condition characterized by multiple congenital anomalies. Typical features include mild global developmental delay, ptosis, and distinctive dysmorphic craniofacial abnormalities, such as metopic ridging or synostosis, and a triangular-shaped forehead with or without autistic features. Brain imaging may reveal abnormalities in the corpus callosum; however, developmental delays may present as global, motor, or speech delays. Additional features may include ear anomalies, feeding difficulties, or congenital heart defects (1,2).

The syndrome is inherited in an autosomal dominant manner, demonstrating complete penetrance but variable expressivity within and across affected families. The syndrome is linked to a heterozygous pathogenic variant in the zinc finger protein 462 gene (*ZNF462*, MIM#617371) and deletion of the 9q31.2 chromosome region involving *ZNF462* (3). To date, only 30 affected individuals from 28 families have been described, no genotype-phenotype correlations have been identified (2,3,4,5,6,9), and the underlying mechanisms remain unclear. With the increasing number of cases worldwide, the original phenotype has expanded, including several complications, such as complete growth hormone deficiency associated with empty sella syndrome (7), Kallmann syndrome (8), and oncological diseases (10).

This study describes a patient with WSKA from Northern China, caused by a novel *de novo* splicing variant in the *ZNF462* gene. A secondary aim of the report is to improve the clinical diagnosis and management of this very rare syndrome by reviewing and analyzing previously reported cases to describe the clinical and molecular characteristics of WSKA.

Case Report

The patient was a 9-year-9-month-old boy admitted to the Department of Endocrinology and Metabolism at Beijing Children's Hospital (Beijing, China) for evaluation of growth retardation as his growth velocity (GV) was 3-4 cm/year, which is below the normal range for his age (GV 5-7cm). He was the second child of healthy, non-consanguineous Chinese parents with no previous abortions and a well-controlled, echographically normal pregnancy. The family had no history of congenital malformations, short stature, intellectual disability, autism spectrum disorder, or other genetic disorders. The first child of this family was a healthy boy without any growth or developmental issues, but he unfortunately died in an accident at 15 years of age. The patient was born at full term via vaginal delivery, with a birth weight of 3.25 kg [-0.175 standard deviation score (SDS)] and a length of 50 cm (-0.22 SDS). No postnatal problems, such as microphallus, cryptorchidism, hypoglycemia, prolonged jaundice, or hypotonia, were reported. He had no history of trauma or chronic illnesses. According to his parents, he could sit and walk unassisted at 8 months and 18 months of age, respectively. However, his language development was delayed when he was young. He started to gain his adult dentition at 8 years of age. He was a picky eater and ate little food but had normal daily activities and sleep duration. No additional congenital anomalies, such as congenital heart defects, optic nerve hypoplasia, papilledema, or hearing impairment, were reported. The patient had no mild hypotonia or other neurological symptoms.

Physical examination: The patient weighed 22 kg (<3rd percentile, -1.87 SD), and his height was 125.6 cm (<3rd percentile, -2.21 SD) at the first visit. The heights of his father and mother were 172 cm and 162 cm, respectively, giving a mid-parental height of 173.5±5 cm. His height was -2.27 SDs below the expected range, falling short of the target family height. He had craniofacial anomalies characterized by heavily arched eyebrows, mild bilateral ptosis, inner epicanthal folds, uneven teeth, macrodontia of the upper central incisors, and low-set ears. A transverse palmar crease was observed on his right palm. His pubertal stage was assessed as Tanner Stage 1 for external genitalia development (testis volume, 2 mL) and pubic hair.

Laboratory and imaging analyses: Laboratory test results for routine blood and urine, including liver and kidney function, and electrolyte levels were within the normal range. The thyroid hormone level including thyroid stimulating hormone, free triiodothyronine, free thyroxine was normal. Plasma adrenocorticotropic hormone and serum cortisol levels were normal. His gonadotropin levels were: basal luteinizing hormone, 0.3 mIU/mL; basal serum follicle-stimulating hormone, 0.5 mIU/mL; testosterone, <20 ng/mL; estradiol, <20 pg/mL; human chorionic gonadotropin, <0.1 mIU/mL; which were consistent with prepubertal status. Serum insulin-like growth factor (IGF)-1 and IGF binding protein-3 levels were 73.1 ng/mL (normal range: 74-388 ng/mL) and 2.69 µg/mL (normal range: 1.8-7.1 µg/mL),

respectively. The bone age was 9-10 years, consistent with his chronological age. Electrocardiography revealed sinus rhythm. The Chinese Wechsler Intelligence Scale for children indicated a verbal intelligence quotient score of 68 and a performance intelligence quotient score of 63. Abdominal ultrasonography showed normal liver, gall bladder, pancreas, spleen, and kidneys. Cranial magnetic resonance imaging (MRI) results indicated a small pituitary gland.

Genetic analysis: Trio (proband and both parents) whole-exome sequencing was performed because of the nonspecific dysmorphic features in the patient and a phenotype indistinguishable from many other inherited disorders with growth retardation. Genomic DNA samples were extracted from the peripheral blood of the patient and his parents and sent to an accredited domestic company for commercial sequencing (MyGenostics, Beijing, China). A *de novo* splicing variant, c.6833-2A > T, was identified in the *ZNF462* gene (NM_021224). The variant was identified in heterozygosis in the patient but was absent in his parents. According to the American College of Medical Genetics variant classification guidelines (11), the variant should be classified as "likely pathogenic". It is a splicing variant in a gene where loss of function is a known disease mechanism, and it removes a portion of the protein (< 10%), which has not been established as crucial to its function (PVS1_moderate). The variant was absent in the parents (*de novo* mutation), and there was no family history (PS2); moreover, the variant has not been reported in general population databases (ClinVar, ExAC, gnomAD, 1000 G) (PM2).

Treatment and follow-up: Recombinant human growth hormone (rhGH) therapy was started at a dose of 0.15 IU/kg/day and administered as daily subcutaneous injections. Unfortunately, the family were lost to follow-up because they moved away from Beijing; however, information obtained via telephone follow-up indicated that his GV was faster than before (5 cm/6 months). No adverse events, such as headaches, were reported.

Discussion

WSKA is a rare disorder caused by mutations in the *ZNF462* gene or deletion of the 9p31.2 chromosome region containing the *ZNF462* gene. The worldwide prevalence of WSKA is unknown, with only 30 affected individuals have been described currently (2,3,4,5,6,7,8,10) and there is only one reported case among the Chinese Han population (9). The number of patients with WSKA reported may be far lower than those harboring *ZNF462* gene variation, which may be due to limited awareness of the disease among healthcare providers, the variability in disease phenotypes, and the mild presentation in some patients.

This study described a patient with WSKA from Northern China, presenting with a novel *de novo* splicing variant in the *ZNF462* gene. This case adds to the limited number of reported cases of WSKA globally; previously reported cases were also reviewed and analyzed given the rarity of the diagnosis. All reviewed patients harbored *ZNF462* variants or deletion in the 9q31.2 chromosome region. The reported patients demonstrated an approximately 2:1 female to male incidence and exhibited a broad spectrum of phenotypes. The most prevalent reported characteristics included developmental delay and craniofacial abnormalities (Table 1). Other phenotypes included autism spectrum disorders, feeding issues, brain abnormalities, congenital heart defects, and limb anomalies (1,2,9). Clinical analyses of the individuals were heterogeneous, and not all individuals underwent comprehensive evaluation, such as brain and heart imaging. Thus, the phenotype frequencies shown in Table 1 may be underestimated. Given the prevalence of developmental delay, corpus callosum anomalies, congenital heart defects, and hearing loss, a comprehensive multidisciplinary evaluation is recommended for individuals with loss-of-function variants in the *ZNF462* gene. Such an assessment should include growth and developmental evaluation, physical examination to identify face shape and suture ridging, ophthalmological evaluation, neuropsychiatric evaluation, hearing evaluation, gastrointestinal/feeding evaluation, cardiac examination with echocardiography, brain imaging, and consultation with a clinical geneticist and genetic counselor. As more patients undergo thorough longitudinal studies, future recommendations for targeted management may emerge.

Table 1. Clinical features of patients with Weiss-Kruszka syndrome

Items	n (%)
Sex (F/M)	20/11
Developmental delay	24/31 (77.4)
Autism spectrum disorder	10/31 (32.2)
Craniofacial features	
Ptosis	27/31 (87.1)
Down slanted palpebral fissures	15/31 (48.4)
Cupid's bow	15/31 (48.4)
Arched eyebrows	15/31 (48.4)
Epicanthal folds	14/31 (45.1)
Short upturned nose	12/31 (38.7)
Ears/hearing	17/31 (54.8)
Feeding issues	14/31 (45.1)
Congenital heart disease	8/31 (25.8)
Limb anomalies	7/31 (22.5)
Craniosynostosis/metopic ridging	10/31 (32.2)
Brain abnormalities	9/31 (29.0)

M: male, F: female

Our patient presented with typical craniofacial features previously reported in individuals with WSKA, including heavily arched eyebrows, mild bilateral ptosis, inner epicanthal folds, low-set ears, together with a transverse right-sided palmar crease, developmental delay, and feeding difficulties. However, growth retardation was the chief complaint of this patient. Among the 19 reported cases with available height parameters, six cases (approximately 31.5%) had height/length below the third percentile for the same age and sex, and nine (approximately 47.3%) were below the tenth percentile. Growth retardation may become apparent with age. Of note, three of these 19 with height data were taller, 75th percentile or greater and one patient exceeded the 97th percentile (Supplementary Table 1). Presently, few reports describe adult patients with WSKA, leaving the long-term height prognosis unclear. One paper presented the case of a Korean boy with molecularly confirmed WSKA and primary empty sella syndrome associated with growth hormone deficiency (7). In the present case, the patient had a slightly lower IGF-1 level and smaller pituitary volume, which may be associated with hypothalamic-pituitary dysfunction. Further studies are required to identify the exact mechanisms of growth retardation, and should include GH assessment by stimulation test.

The formal diagnostic criteria for WKSA have not yet been established. WKSA should be suspected in individuals with suggestive clinical and brain MRI findings. Diagnosis is confirmed by identifying a heterozygous pathogenic variant in *ZNF462* or deletion of 9p31.2 including *ZNF462* or, rarely, chromosome rearrangements that disrupt *ZNF462* (1). *ZNF462* is a C2H2-type zinc finger transcription factor with 23 zinc finger domains, making DNA binding a likely function (12). *ZNF462* is essential for embryonic development in multiple species, is involved in chromatin remodeling, and binds *H3K9me3*, making it a chromatin reader involved in heterochromatin modifications (13). *ZNF262* is also necessary for cell division during the cleavage stage (14), helps maintain chromatin structure in pluripotent cells (15), and interacts with the heterochromatin protein 1α (HP1α) (13). As hallmarks of heterochromatin, HP1α and *H3K9me3* are key to gene silencing, repetitive DNA transcription, and genome integrity (16,17,18), further emphasizing the role of *ZNF462* in chromatin remodeling. WKSA occurs via a presumed loss-of-function mechanism, inherited in an autosomal dominant manner, with most pathogenic variants reported in exon 3. However, the molecular mechanism underlying this associated phenotype remains unknown. Most cases (95%) occur because of *de novo* mutations in *ZNF462,* and only 5% of individuals diagnosed with WKSA have an affected parent, with parental germline mosaicism reported in only one family (2). No genotype-phenotype correlations have been identified because familial cases show highly variable expressivity in the phenotypic manifestations, making genetic counseling important for understanding the disease etiology, recurrence risk, and family planning, including prenatal and preimplantation genetic testing. However, because of intrafamilial clinical variability, molecular genetic test results cannot accurately predict clinical findings.

The treatment of WKSA is primarily symptomatic and involves comprehensive clinical multidisciplinary therapy. Only one case report has discussed the effectiveness of growth hormone therapy for short stature (3). In this report, rhGH replacement was initiated at a dose of 0.23 mg/kg/week and was gradually increased to 0.3 mg/kg/week. After two years of treatment, an improvement in height velocity (8 cm/year) was observed, with the height SDS increasing from -3.49 SDS to -1.15 SDS. Our patient was also treated with rhGH but treatment effectiveness could not be determined owing to the short duration of the treatment. Further study of the molecular mechanisms involving *ZNF462* may open new avenues for targeted therapy.

Conclusion

In conclusion, this study describes a Chinese patient diagnosed with WKSA and the genotypic and phenotypic characteristics of all published cases of WKSA. The presented patient provides additional clinical and genetic evidence to support the mechanism of haploinsufficiency of the *ZNF462* gene, as proposed by earlier studies. The novel variant and phenotypes observed in our patient expands the spectrum of clinical features, genetic characteristics, diagnostic protocols, and genetic counseling for WSKA.

Ethics

Informed Consent: This study was approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University (2020-k-139). Written informed consent was obtained from the legal guardian of the participant. This study was conducted in accordance with the principles of the Declaration of Helsinki.

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Footnotes

Authorship Contributions

Concept: Chunxiu Gong, Design: Chunxiu Gong, Data Collection and Processing: Chunxiu Gong, Analysis or Interpretation: Lele Li, Literature Search: Lele Li, Writing: Lele Li.

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Supplementary Table: https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/c28950ce-ed26-446f-b42f-0523dbd8b60d.pdf

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