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The role of SLC12A3 gene variant c.1964G > A in co-existing Gitelman syndrome and unilateral limb paralysis: a case report and literature review

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Abstract

We report a Gitelman syndrome (GS) pedigree from a Chinese family. The proband, a middle-aged man, presented with hypokalemia, hypomagnesemia, and unilateral limb paralysis. After a comprehensive evaluation, peripheral neuropathy and the cranial or spinal cord disorders were ruled out. Genetic testing identified a homozygous c.1964G > A variant in the SLC12A3 gene. Despite potassium and magnesium supplementation, the patient's clinical symptoms persisted. Additionally, 13 heterozygous family members, including his parents, showed no typical GS manifestations. However, the proband's two brothers, who also carried the same homozygous mutation and exhibited hypokalemia and hypomagnesemia, did not develop unilateral limb paralysis. This case suggests that the c.1964G > A variant may be associated with a severe GS phenotype, including unilateral limb paralysis. Clinicians should be aware of the diagnostic challenges and therapeutic limitations in managing GS, particularly in patients with severe manifestations. Genetic testing is essential for accurate diagnosis, and ongoing monitoring and symptomatic management are critical to improving the quality of life for affected individuals.

Keywords Gitelman syndrome, Unilateral limb paralysis, SLC12A3, c.1964G > A

Introduction

Gitelman syndrome (GS: OMIM 263800) is a rare autosomal recessive hereditary salt-losing renal tubular disease first described by Gitelman et al. in 1966 with a prevalence of approximately 1/40,000 to 1/4,000 [1, 2], possibly higher in Asian populations [3, 4]. It is one of the most common causes of inherited hypokalemic and hypomagnesemic disorders, and other clinical manifestations include normal or low blood pressure, activation of the renin-angiotensin-aldosterone system (RAAS), metabolic alkalosis, hypochlorhydria, and low urinary calcium. The syndrome is caused by an inactivation mutation of the SLC12A3 gene located on chromosome 16q13, which leads to dysfunction of the thiazide-sensitive sodium-chloride cotransporter (NCCT) expressed at the tip of the membrane of the distal renal tubules. Patients with mild cases have no obvious symptoms while severe cases may experience limb convulsions, soft paralysis, painful spasm, syncope, rhabdomyolysis secondary to acute kidney injury, and even severe ventricular arrhythmia. The diagnosis of GS is confirmed through clinical manifestations, biochemical abnormalities, and genetic testing for mutations in the SLC12A3 gene. Despite the chronic

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nature of the disease, appropriate management with electrolyte supplementation can significantly improve the quality of life for affected individuals.

GS symptoms are mostly systemic and symmetrical, severe manifestations of unilateral limb disorders in GS patients have rarely been reported. Here, we report a 43-year-old male diagnosed with GS combined unilateral disturbance, presenting with a history of the superficial and deep sensations of the left limb decreased significantly compared to his right limb. We ruled out neurological diseases and analyzed phenotype and genotype of the Chinese pedigree with GS. This case underscores the importance of considering GS in the differential diagnosis of patients with persistent hypokalemia and unilateral limb paralysis, especially when standard treatments fail to yield significant improvements. The rarity of GS, coupled with its potential for severe complications, highlights the critical need for awareness and timely diagnosis among clinicians.

Table 1 Biochemical characteristics of the proband

Examination item	Test value	Reference value
Serum biochemicals		
Potassium (mmol/L)	2.87	3.50–5.50
Sodium (mmol/L)	138	137–147
Chloride (mmol/L)	96.8	96.0-108.0
Calcium (mmol/L)	2.41	2.11–2.52
Phosphate (mmol/L)	1.11	0.85–1.51
Magnesium (mmol/L)	0.54	0.75–1.02
Creatine (μmol/L)	60.0	57.0–97.0
BUN (mmol/L)	7.1	3.1-8.0
free triiodothyronine (pg/mL)	2.93	2.00-4.40
free tetraiodothyronine (ng/dL)	1.48	0.93–1.70
thyroid-stimulating hormone (uIU/mL)	1.00	0.27–4.20
Arterial blood gas analysis		
PH	7.49	7.35–7.45
PO_2 (mmHg)	93.0	83.0-108.0
PCO_2 (mmHg)	36.9	35.0–45.0
Base excess (mmol/L)	5.0	-2.0-3.0
TCO_2 (mmol/L)	29.0	23.0–27.0
Urine tests		
Urine specifific gravity	1.018	1.003–1.030
Urine PH	6.0	4.5-8.0
Potassium (mmol/24 h)	75.82	25.00-100.00
Calcium (mmol/24 h)	1.24	2.50–7.50
Phosphate (mmol/24 h)	34.91	16.00–42.00
Creatinine (umol/24 h)	8823	8800–17,600
RASS system		
Plasma renin activity (ng/mL.h)	5.02	0.20–1.90
Aldosterone (ng/dL)	18.06	2.94–16.15
ARR (ng/dL: ng/mL.h)	3.60	

Case presentation

The proband was a 43-year-old male who reported that 13 years earlier, he had experienced limb weakness, myalgia, and sweating skin due to a cold. The above symptoms subsequently worsened, leading to temporary limb paralysis and difficulty speaking. After visiting a local hospital, he was diagnosed with potassium deficiency, and his symptoms improved with potassium supplements. The patient had been a driver for an extended period of time. Since 2016, he had experienced difficulty with the left foot clutch and began to use a crutch to help him walk. For the past two years, the patient has experienced significant sensory weakness in his left limb and has been unable to stand, requiring a wheelchair for daily activities. He also presented with muscle pain, palpitations, and chest tightness, and his lowest blood potassium was 2.4 mmol/L. The results of the lumbar punctures and computed tomography scan of the adrenal glands were normal. Potassium chloride sustained-release tablets (1.0 g) were administered orally 5–6 times/day, but muscle pain and palpitations symptoms did not completely improve. The patient was conscious and stable following a comprehensive assessment of his medical history, and he reported that his family members did not have similar clinical symptoms.

We conducted a thorough physical examination on the first day of the patient's admission to our hospital. His temperature was 36.8 ℃, blood pressure was 114/81 mmHg, heart rate was 80 beats/min, respiratory rate was 18 breaths/min, and body mass index was 23.5 kg/m^2. On neurological examination, his pain and temperature perception of the facial and limb, sense of touch and position were weakened to some extent, particularly on the left side. His muscle strength was graded as follows: right upper limb 5, left upper limb 3, right lower limb 5–, and left lower limb 2.

The patient's laboratory tests suggested hypokalaemia, metabolic alkalosis, and RAAS activation, along with hypomagnesaemia and decreased urinary calcium excretion, as shown in Table 1. His liver function, thyroid and gonadal hormones, and the circadian rhythm of plasma cortisol were within the normal range. Electrocardiogram showed sinus rhythm, heart rate 74 bpm. The patient's electromyography (EMG) showed normal status of motor and sensory conduction velocities, F-waves and H-reflexes, and with no evidence of forceful contraction of the examined muscle. In addition, a thorough neurological assessment was carried out. The cranial and spinal cord diseases, peripheral neuropathy, and other neurological disorders were ruled out by the normal results of the electroencephalogram, transcranial Doppler, magnetic resonance imaging (MRI) of the head, cerebrovascular, cervical and lumbar spine, vestibular function and audiometry, and myoglobins of blood and urine.

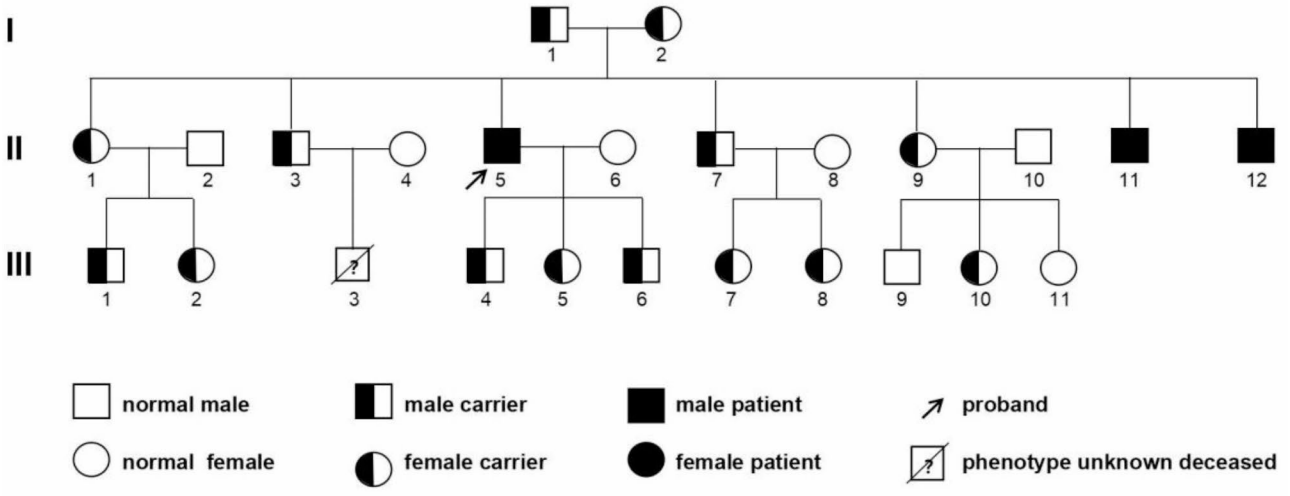

Fig. 1 Pedigree chart of the proband's family (II_5, the proband)

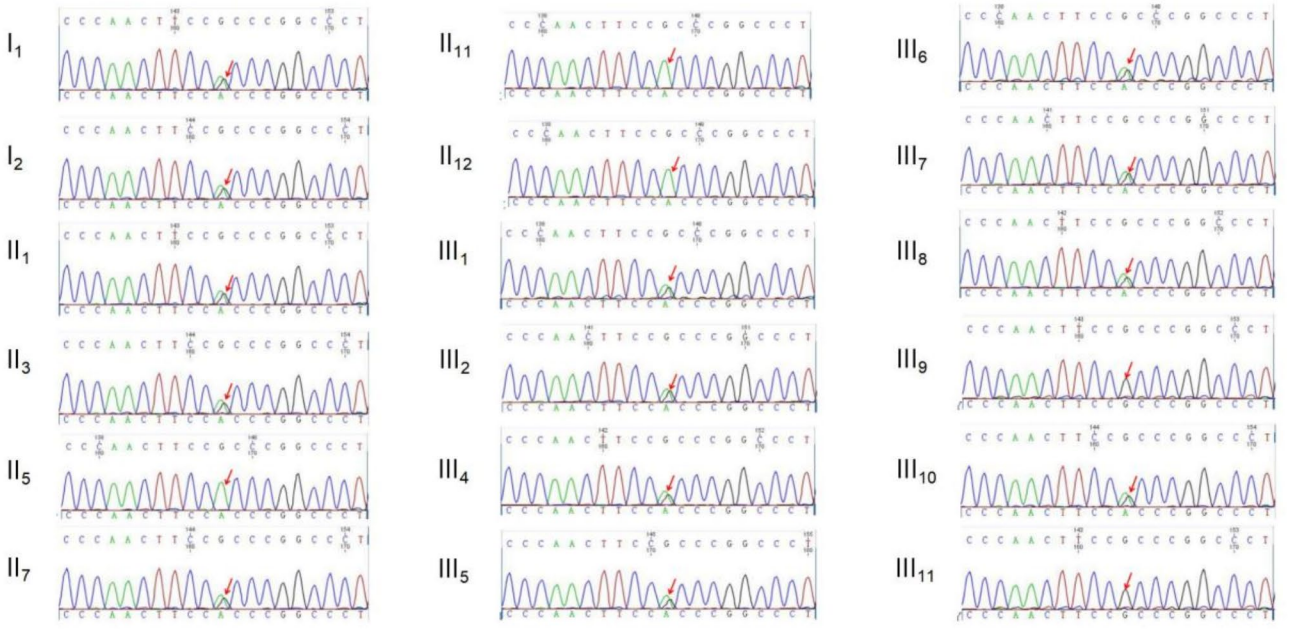

Fig. 2 Genetic sequencing results on the SLC12A3 gene of the proband and his family members. indicate that homozygous variant c.1964G > A in the proband (II_5) and his two younger brothers (II_{11-12}), heterozygous variant in I_{1-2}, II_1, II_3, II_7, III_{1-2}, III_{4-8}, and III_{10}, and non-carrier in the remaining family members

Combining the manifestations and biochemical parameters, the patient was clinically diagnosed with GS. Next-generation panel sequencing for hyperkalemia was then performed to further clarify the genetic diagnosis. Peripheral blood samples were collected for DNA extraction using standardized EDTA-2Na protocols and commercial kits. In items of screening the patient (proband II_5), the Roche Nimblegen SeqCap EZ Choice XL Library (Roche Sequencing and Life Science, Indianapolis, IN, USA) was used for exon capture (containing 4431 genes), and the Illumina sequencing platform (Illumina, San Diego, CA, USA) was used for high-throughput sequencing. PCR amplification and Sanger sequencing were performed on the patient's family. Informed consent was obtained from all individual participants in the study.

Figure 1 presents the patient's pedigree. Figure 2 provides the results of the SLC12A3 gene sequencing. Table 2 summarizes the genetic findings and electrolyte levels in the proband and his family members. The patient's c.1964G > A homozygous mutation modifies the amino acid p.Arg655His. No other significant variant was detected that could explain the patient's findings. His two younger brothers were also homozygous and also had moderate electrolyte disturbances. The blood potassium

Table 2 Main laboratory results and SLC12A3 gene variant of pedigree members

Family members	Potassium (mmol/L)	Sodium (mmol/L)	Chloride (mmol/L)	Calcium (mmol/L)	Phosphate (mmol/L)	Magnesium (mmol/L)	TCO2 (mmol/L)	SLC12A3 variant (c.1964G > A)
Father (I_1)	4.18	140	101.4	2.48	1.04	1.05	25.39	Het
Mother (I_2)	5.42	138	104.4	2.52	1.53	1.07	18.87	Het
First sister (II_1)	4.83	142	107.4	2.54	1.24	1.12	21.36	Het
First brother (II_3)	4.49	143	106.0	2.47	0.90	1.11	23.35	Het
Second brother (II_7)	4.31	141	105.9	2.39	1.22	0.90	20.35	Het
Third brother (II_{11})	4.49	138	92.5	2.62	0.71	0.74	28.79	Hom
Fourth brother (II_{12})	3.24	142	95.2	2.59	0.93	0.96	27.48	Hom
Nephew (II_{11})	4.59	141	103.5	2.56	1.14	0.94	23.54	Het
Niece (II_{12})	4.99	138	102.1	2.36	1.32	0.93	22.65	Het
First son (III_4)	4.82	140	107.9	2.40	1.62	1.06	19.90	Het
Daughter (III_5)	4.40	140	103.9	2.33	1.96	0.97	20.14	Het
Second son (III_6)	5.14	140	105.1	2.41	1.83	1.07	18.77	Het
Niece (III_7)	4.38	139	101.5	2.49	1.60	0.93	21.23	Het
Niece (III_8)	4.31	143	109.5	2.61	1.89	0.97	16.41	Het
Nephew (III_9)	3.81	141	104.4	2.40	1.35	0.96	20.34	None
Niece (III_{10})	4.39	139	103.6	2.42	1.83	0.90	19.04	Het
Niece (III_{11})	4.69	139	103.3	2.47	1.95	0.94	17.50	None
Reference value	3.50–5.50	137–147	96.0-108.0	2.11–2.52	0.85–1.51	0.75–1.02	23.00–27.00	

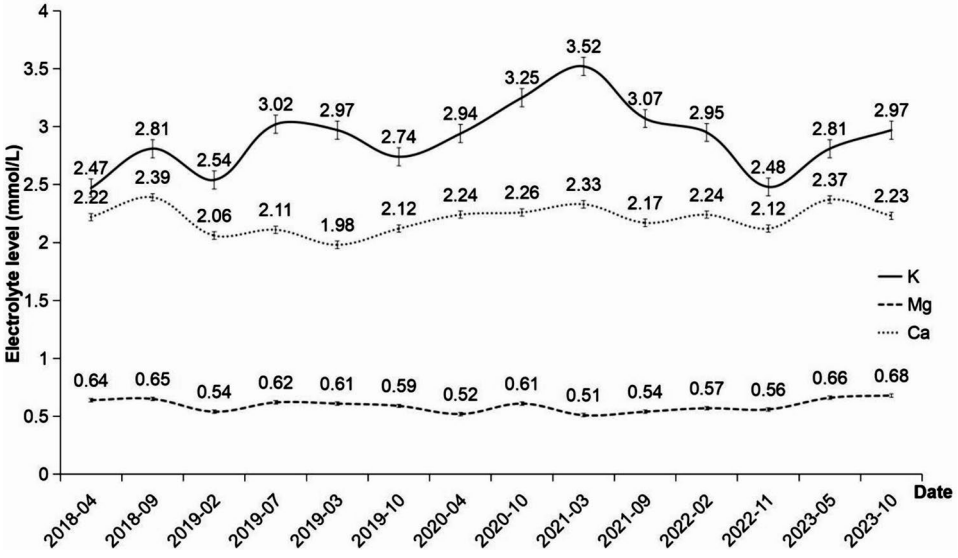

Fig. 3 Follow-up variations in the proband's electrolyte levels of potassium, magnesium and calcium

level of the fourth brother (II_{12}) was 3.24 mmol/L and the blood magnesium level of the third brother (II_{11}) was 0.74 mmol/L. The oldest brother's son (II_3) died of hypokalemia (unknown genetic abnormality) at the age of 12. The remaining 13 family members were heterozygous carriers, including the patient's parents. They did not have nocturia, fatigue, thirst, muscle spasms, or other symptoms associated with GS, and their medical examinations were unremarkable.

Oral potassium chloride sustained-release tablets, potassium magnesium aspartate tablets, and spironolactone tablets were used to supplement electrolytes after the patient was diagnosed with GS. Indomethacin, a prostaglandin synthase inhibitor, was given to the patient in small doses to relieve symptoms of severe myalgia and muscle weakness. However, the proband was first referred to our hospital for treatment in 2018, and during the next 6 years of follow-up, monitoring of electrolyte disturbances remained below the lower limit of normal, as shown in Fig. 3, and unilateral limb paralysis never improved despite supplementation with magnesium oxide (800 mg/day Nature Made) for hypomagnesemia. The patient had a long history of stomach pain and arrhythmia, and his quality of life was gradually

deteriorating. In the past two years, new symptoms have appeared, including severe anxiety, insomnia, intermittent headaches, and a fatty liver. At present, he is actively receiving appropriate medication to control the above symptoms. We have continued to follow other family members and no new clinical phenotypes have been identified.

Discussion

GS is an autosomal recessive disorder caused by inactivating mutations in the SLC12A3 gene, which encodes NCCT expressed in the distal convoluted tubule (DCT) of the kidney [5, 6]. NCCT dysfunction leads to impaired sodium reabsorption, hypokalemia, hypomagnesemia, hypocalciuria, and metabolic alkalosis. The DCT is responsible for 5–10% of renal sodium reabsorption [7], and defective NCCT function increases sodium delivery to the collecting duct, promoting potassium and hydrogen excretion. This process is exacerbated by secondary hyperaldosteronism due to chronic volume contraction caused by salt wasting [8]. Hypomagnesemia in GS is linked to the downregulation of the epithelial magnesium channel transient receptor potential cation channel subfamily M member 6 (TRPM6) [9–11], which is co-localized with NCCT in the DCT. The functional status of NCCT may regulate TRPM6, explaining why patients with hypomagnesemia often exhibit more severe symptoms. Reduced systemic magnesium concentrations can lead to impaired neurological and cardiovascular system function [12]. The mechanism of hypocalciuria remains controversial but may involve increased expression of calcium channels, TRPV5 and TRPV6, in the DCT [13, 14]. These pathophysiological changes contribute to the characteristic biochemical profile of GS and its clinical manifestations.

To date, nearly 570 different mutations in the SLC12A3 gene have been identified in GS (https://www.ncbi.nlm.nih.gov/clinvar), including missense, nonsense, frameshift , and deletion mutations. Researchers have utilized bioinformatics tools to predict the pathogenicity of newly discovered mutations, analyzed the structural stability of these mutant proteins in both 2D and 3D, and subsequently refined animal or cellular functional assays for validation [15]. In China, common mutations such as T60M, D486N, T163M, R913Q, R928C, and R959frameshift have allele frequencies greater than 3% [16–19]. A review of SLC12A3 missense and nonsense mutations from the HGMD revealed that variants in Asian GS patients were widely dispersed throughout the gene, while in European and American GS patients were concentrated in the transmembrane region and intracellular segment. The proband in this study carried c.1964G > A variant, located in the intracellular segment of NCCT. This variant was first reported in 1996 and is classified as pathogenic or likely pathogenic according to the American College of Medical Genetics and Genomics (ACMG) guidelines [20, 21].

GS typically presents in adolescence or adulthood with no obvious or mild symptoms such as muscle weakness, fatigue, salt cravings, and nocturia. However, some patients exhibit severe phenotypes, including early-onset disease (before age 6), developmental delays, rhabdomyolysis, renal insufficiency, and ventricular arrhythmias [22]. Cruz et al. found that approximately half of the participants reported experiencing moderate to severe symptoms, which negatively impacted their quality of life [23]. Extra-renal manifestations, such as short stature, thyroid disorders (hyperthyroidism or hypothyroidism), and abnormal glucose tolerance, have also been reported [24–28]. Studies indicate that homozygous patients usually have a more severe clinical phenotype than heterozygous patients [29]. The specific impact of mutations, such as c.1964G > A (Arg655His), can vary due to factors including the location and nature of the mutation's impact on protein function. The c.1964G > A may contribute to a more severe phenotype, as evidenced by the proband`s unilateral limb paralysis, a rare neurological manifestation in GS. The relationship between genotype and phenotype in GS is complex, and factors such as modifier genes, epigenetic influences, and environmental triggers may further contribute to phenotypic variability [30, 31].

The proband's clinical course was characterized by prolonged and severe hypokalemia and hypomagnesemia, which probably exacerbated the neurological deficits, including unilateral limb paralysis and sensory impairment. While these symptoms are atypical for GS, they may result from chronic electrolyte imbalances and secondary complications. Neurological evaluations ruled out the causes of neuropathy and confirmed the diagnosis of GS. The relationship between specific SLC12A3 mutations and clinical severity remains incompletely understood. Liu et al. suggested that patients with severe mutations in both alleles often exhibit higher urinary fractional excretion of potassium, magnesium, and chloride, leading to more pronounced symptoms [17]. Eva et al. proposed that the nature and position of SLC12A3 mutation, combined with male gender, is a determinant factor in the severity of GS. Phenotypic variability is influenced by factors such as mutation location, environmental triggers, and modifier genes. The genetic analysis of the proband's family revealed that two of his younger brothers also had the same homozygous mutation of c.1964G > A, suggesting a hereditary pattern and moderate electrolyte disturbances without weakness, pain, convulsions, hypoesthesia, or dyskinesia, which need to be clarified by further regular follow-up. The death

of a nephew from hypokalemia further underscores the potential severity of untreated or poorly managed GS.

Most patients with GS have atypical symptoms that complicate diagnosis without genetic evidence, even when medical history, laboratory tests, and imaging examinations are available. With the rapid development of gene sequencing technology, there has been an increase in number of patients with hypokalemia who have been diagnosed with GS. The management of GS primarily involves lifelong supplementation with potassium and magnesium, dietary modifications, and, in some cases, potassium-sparing diuretics or nonsteroidal anti-inflammatory drugs (NSAIDs) like indomethacin to reduce symptoms [32–35]. Despite these interventions, the proband's symptoms persisted, highlighting the challenges of managing chronic electrolyte imbalances in GS. Potential reasons for treatment resistance include noncompliance, malabsorption, or the presence of additional genetic or environmental modifiers.

The proband's development of severe anxiety, insomnia, and fatty liver further underscores the need for comprehensive management strategies that address both the primary and secondary complications of GS. Current treatment protocols have significant limitations, and future research should focus on optimizing therapeutic approaches, such as targeted therapies or advanced electrolyte monitoring, to improve patient outcomes.

Conclusions

GS is a genetically heterogeneous disorder with significant phenotypic variability. The c.1964G > A mutation in the SLC12A3 gene may contribute to severe neurological manifestations, as observed in the proband's case. This report underscores the complexity of GS and the importance of comprehensive management strategies, including genetic counseling for affected families. Ongoing monitoring and individualized treatment adjustments are essential to manage symptoms and improve quality of life. Future research should aim to elucidate the mechanisms underlying genotype-phenotype relationships and develop targeted therapies to address the unmet needs of GS patients.

Abbreviations

GS	Gitelman syndrome
RAAS	Renin-angiotensin-aldosterone system
NCCT	Sodium-chloride cotransporte
DCT	Distal convoluted tubule
EMG	Electromyography
MRI	Magnetic resonance imaging

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Author contributions

Material preparation, data collection, and literature search were performed by Fuhui Ma and Rui Ma. The first draft of the manuscript was written by Fuhui Ma, and all authors commented on previous versions of the manuscript. Fuhui Ma, Wusiman Reziwanguli, and Kaidi Zhang provided diagnoses and treatments to the patients reported in this study. Xinling Wang and Yanying Guo supervised the manuscript drafting. All authors have read and agreed to the published version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region (No.KY2021052650). All methods were performed in accordance with the Declaration of Helsinki, and written informed consent for publication was obtained from all the participants.

Consent for publication

Written informed consent was obtained from the patient for the publication of any related images or data included in this manuscript. For patient's families under the age of 18, written informed consents for the publication of any related images or data were obtained from their parents.

Competing interests

The authors declare no competing interests.

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