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Gitelman Syndrome Combined with Congenital Chloride Losing Diarrhea Owning to Defective SLC12A3 and SLC26A3

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Abstract

Introduction: Gitelman Syndrome (GS) is a hypokalemic metabolic alkalosis with significant hypomagnesemia, and low urinary calcium excretion and is associated with a biallelic inactivating mutations of the *SLC12A3* gene. Congenital Chloride-Losing Diarrhea (CCLD) is characterized by watery diarrhea with a high level of fecal Cl^-, metabolic alkalosis, and electrolyte alterations and is caused by mutations in the *SLC26A3* gene, which encodes the intestinal Cl-/$HCO3^-$ exchanger. Both GS and CCLD are rare. We herein report a case combined with both GS and CCLD.

Methods: A 24-year-old female patient was hospitalized for evaluation because of recurrent hypokalemia, and numbness in hands, feet, and chest. We first performed clinical manifestation and biochemical examination and then carried out genomic DNA sequencing analysis.

Results: The heterozygote variants of *SLC12A3* (c.1456G>A, p.D486N), *SLC26A3* (c.632G>C, p.S211T), CFTR (c.480T>G, p.I160M) and *CLDN16* (c.458T>C, p.I153T) were identified and the related protein structures were analyzed. *SLC12A3* gene mutation caused a decrease in the recovery of Na^+, Cl^- and K^+ in the distal convoluted tubules of kidneys, while the *SLC26A3* gene mutation led to a decreased absorption of Cl^- and K^+ into blood circulation and an increase in fecal excretion.

Conclusion: We have diagnosed the case with GS and CCLD owning to defective *SLC12A3* and *SLC26A3* and discussed the clinical phenotypes in this case, mainly including hypokalemia and watery diarrhea.

Keywords: Congenital chloride diarrhea; Gitelman syndrome; SLC12A3; SLC26A3

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Abbreviations

AR: Autosomal Recessive inherited mode; CCLD: Congenital Chloride Losing Diarrhea; GS: Gitelman Syndrome; SLC12A3: Solute Carrier Family 12 member 3; SLC26A3: Solute Carrier family 26 member 3; CFTR: CF Transmembrane Conductance Regulator; CLDN16: Claudin 16

Introduction

Gitelman Syndrome (GS) is clinically characterized by hypokalemia, hypomagnesemia, hypocalciuria, and metabolic alkalosis [1,2]. Genetically, GS is caused by an inactivating mutation in the solute carrier family 12-member 3 (*SLC12A3*) gene. *SLC12A3* is encoded for the thiazide-sensitive Sodium-Chloride Cotransporter (NCCT), highly expresses in expressed in the Distal Convoluted Tubule (DCT) of kidneys and functionally mediates Na+ and Cl- reabsorption in DCT cells of kidneys [2-4]. An experimental study has previously shown that with the knockdown of zebrafish ortholog, slc12a3 led to structural abnormality of kidney pronephric distal duct at 1-cell stage, suggesting that *SLC12A3* may have genetic effects in renal disorders [5]. Accumulating genetic studies have demonstrated that GS is one Autosomal Recessive (AR) inherited disease and is associated with a biallelic inactivating mutation of the *SLC12A3* gene.

Congenital Chloride Losing Diarrhea (CCLD, also known as congenital secretory chloride diarrhea 1, DLAR1) is another AR disorder and caused by mutations in the solute carrier family 26-member 3 (*SLC26A3*) gene. *SLC26A3* is a member of the SLC26 sulfate permease/anion transporter family. This gene is expressed mainly in the apical brush border of the intestinal epithelium and encodes the intestinal Cl-/$HCO3^-$ exchanger. The only extraintestinal tissues showing *SLC26A3* expression are eccrine sweat glands and seminal vesicles [6-9]. Therefore, CCLD is a disorder of

intestinal electrolyte absorption and clinically characterized by watery diarrhea with a high level of fecal Cl^-, metabolic alkalosis, and electrolyte alterations.

Both GS and CCLD are rare, while the case where these two disorders are combined is even rarer. Over the past year, we have received a case in the inpatient department of our hospital, which is a mixture of GS and CCLD. In the current study, we first represent the clinical examination of this patient. We then report the data of molecular diagnosis by using genomic DNA sequencing and diagnosed the patient with GS and CCLD owning to heterozygote variants of the *SLC12A3* and *SLC26A3* genes. Finally, we discuss the main phenotypes of this patient including hypokalemia and watery diarrhea and our working experience in diagnosing and treating such rare and complex cases, which may benefit clinicians and researchers in the outpatient and scientific works.

Subject and Methods

The patient is a Han Chinese woman, 24 years old and married and she visited our hospital on July 21st, 2020. At the time of admission, the patient was seen to be thin, with a weight loss of 15.5 kg compared with that before pregnancy. She had numbness of hands and feet, convulsions of calf muscles, conscious numbness and palpitation in the chest, dizziness, fatigue, and syncope in severe cases; irritability and insomnia; thirst and drunk, with acceptable appetite, long-term diarrhea, stool-forming polyuria, 7 to 8 times a day but no nausea and vomiting, no cough and chest pain, no abdominal pain and distension, no chills and fever. We gave her a full physical and biochemical examination and the data are summarized in Table 1A.

Two years before she visited our hospital, she suffered from amniotic fluid embolism and coma after giving birth to a girl in a local hospital. After recovered, she was discharged from the hospital. Three months later, the patient went to the same local hospital again for treatment due to numbness of hands and feet. In the hospital, biochemical examination mainly showed that her blood potassium level was 2.2 mmol/l ↓, and blood chlorine level was 87.0 mmol/l ↓. She was then diagnosed as "hypokalemia" and admitted to the hospital. The medical treatment included "potassium chloride sustained release tablets" orally and potassium chloride injection intravenously to supplement potassium. After treatment, her blood potassium retest became normal. One week after the patient was discharged from the local hospital, however, her blood potassium level was decreased again, and blood potassium level was still very low, i.e. 2.2 mmol/l to 2.6 mmol/l. Since then, the patient repeatedly visited the local hospital for potassium supplement treatment. A historical record of the dynamic changes of potassium, chloride and bicarbonate levels in her serum samples is represented in Table 1B.

To analyze the inheritable disorders with complicated genetic heterogeneity in an efficient way, our hospital laboratory department has cooperated with MyGenostics, (Beijing, China), which has produced a series of gene capture panels specifically for different types of genetic diseases. We employed MyGenostics Inheritable Diseases panel to target sequence several diseases causing genes quickly and precisely. First, genomic DNA was extracted from peripheral blood leukocytes. The DNA library was then hybridized with target enrichment capture probes according to the MyGenostics GenCap enrichment standard protocol (http://www.mygenostics.com). Finally, the hybrid products were purified and sequenced using an Illumina HiSeq2000 PEI101 (Illumina, San Diego, USA). Based

Table 1A: Clinical manifestation and biochemical examination.

Clinical parameter	Normal range	Patient value
Sex		Female
Age (year)		24
High (cm)		163
Body weight (kg)		41.5
BMI (kg/m^2)		15.62
SBP (mmHg)		102
DBP (mmHg)		74
Heart rate (/min)		100
Respiratory rate (/min)		20
Body temperature (ºC)		36.5
Arterial blood gas analysis		
pH	7.35-7.45	7.475 ↑
K+	3.4-4.5 mmol/L	2.8 mmol/L ↓
Na+	135-145 mmol/L	137 mmol/L
Ca+	1.15-1.29 mmol/L	1.12 mmol/L
Cl-	98-106 mmol/L	93 mmol/L
HCO3-	21-28 mmol/L	38.0 mmol/L ↑
SBE	-3-3 mmol/L	14.5 mmol/L ↑
Lac lactic acid	0.5-1.7 mmol/L	0.7 mmol/L
Biochemical examination		
Serum sodium	136.0-145.0 mmol/L	135.8 mmol/L ↓
Serum potassium	3.50-5.10 mmol/L	2.32mmol ↓
Serum chloride	98.0-107.0 mmol/L	87.1mmol ↓
Serum adjusted calcium	2.10-2.55 mmol/L	2.47mmol
Serum magnesium	0.70-1.00 mmol/L	0.82mmol
serum phosphorus	0.81-1.45 mmol/L	1.29mmol
CO_2	22.0-30.0 mmol/L	43.4mmol ↑
24h urine biochemical analysis		
Urine potassium	25-100 mmol/24 h	68.1 mmol/24 h
Urine sodium	130-260 mmol/24 h	784.1 mmol/24h
Urine magnesium	3.0-4.5 mmol/24 h	5.0 mmol/24 h
Adrenal cortex function and rhythm		
Cortisol	-	-
08:00	8.7-22.4 μg/ul	10.4 μg/ul
16:00	<10.0 μg/ul	10.0 μg/ul
24:00	-	1.7 μg/ul
24-hour urinary free cortisol	58-403 μg/24 h	329.7 μg/24h
Adrenocorticotropic hormone		
08:00	0.00-46.00 pg/ml	33.49
16:00	0.00-46.00 pg/ml	23.9
24:00	0.00-46.00 pg/ml	5.43
Activity of angiotensin aldosterone system		
Renin	0.13-1.74 ng/ml/h	1.61 ng/ml/h
Angiotensin II	-	-
Aldosterone	30-180 ng/L	206.39 ng/L
24h ambulatory blood pressure monitoring		hypotension

Color ultrasound of kidney and ureter		normal
Renicapsule plain and contrast enhancement CT scan		normal
Electrocardiogram		normal

All data are recorded in our department of endocrinology when the patient is hospitalized for the first time in July 2021.

Table 1B: Serum potassium, chloride, and bicarbonate levels and their dynamic changes.

Date	Serum potassium (mmol/L) (Normal range 3.50-5.50)	Serum Chloride (mmol/L) (Normal range 96.00-106.00)	Serum Bicarbonate (mmol/L) (Normal range 22.00-27.00)
2018-06-30	4.20	107.60	-
2018-07-22	3.80	107.50	-
2018-11-13	2.20	87.00	-
2018-11-22	2.48	91.70	-
2020-07-21	2.79	91.60	-
2021-03-26	2.96	93.60	34.70
2021-09-07	2.87	96.10	30.70
2021-10-24	2.60	-	-
2022-03-28	3.10	-	-
2022-06-27	2.38	-	32.40

Note: The numbers in italics are the data before the patient suffered from amniotic fluid embolism and coma after giving birth to a girl.

on the information from OMIM (Online Mendelian Inheritance in Man) database, a total of 67 known genes in which the mutations might cause hypokalemia were selected. We performed the capture sequencing analysis on the exons and splicing regions of these 67 genes in the current study and a list of the studied genes is summarized in Table 2.

To evaluate the biological effects of *SLC12A3* and *SLC26A3* variants, we used the protein molecular modeling program of the Swiss-model (https://swissmodel.expasy.org/) and performed the analyses based upon the template from the AlphaFold protein structure database (https://alphafold.ebi.ac.uk/) [10,11].

Results and Discussion

In the current study, the female patient has two gene mutations i.e., *SLC12A3* (p.D486N) and *SLC26A3* (p.S211T), which lead to the superposition of intestinal and renal potassium loss, resulting in long-term chronic hypokalemia and metabolic alkalosis. The condition is serious, even though replacement and supplement of potassium. It is difficult to reverse the loss of kidneys and intestines.

The clinical characteristics of the patient are relatively complex. To better diagnose and treat, we adopted G.DNA sequencing technology as a molecular diagnosis. We found that there were the missense mutations in four genes, including *SLC12A3* (c.1456G>A, p.D486N), *SLC26A3* (c.632G>C, p.S211T), *CFTR* (c.480T>G, p.I160M) and *CLDN16* (c.458T>C, p.I153T). The details of related genes and their mutations are summarized in Table 3. All genotypes of these mutations in the genes are heterozygotes. We further analyzed whether the mutations D486N in *SLC12A3* and S211T in *SLC26A3* might lead to the changes in protein structure with the AlphaFold program, and the results implicated that these variations could cause dysfunction of the proteins (Figure 1).

The illness onset of these patients is special. GS is often presented

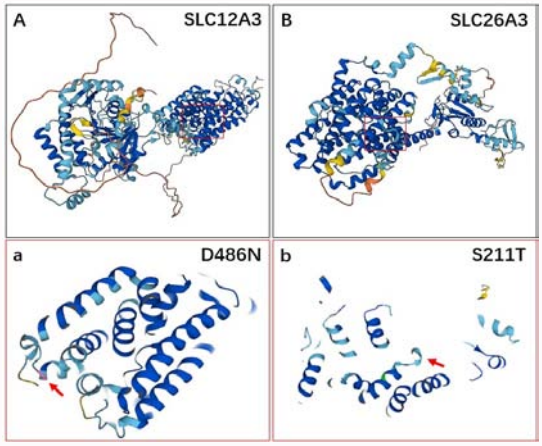

Figure 1: Effects of SLC12A3 and SLC26A3 mutations in protein structure. A&B The schematic diagrams have shown that the protein structures (3-D) of the *SLC12A3* and *SLC26A3* genes, respectively. Topological analyses have indicated that one missense mutation D486N (a) results in the change of cytoplasmic topological domain in SLC12A3 (AF-P55017-F1, Confidence score 85.54), while another missense mutation S211T (b) led to the change of helical transmembrane in SLC26A3 (AF-P40879-F1, Confidence score 92.41). The changes of SLC12A3 and SLC26A3 protein structure with each missense mutation are predicted respectively by using the AlphaFold.

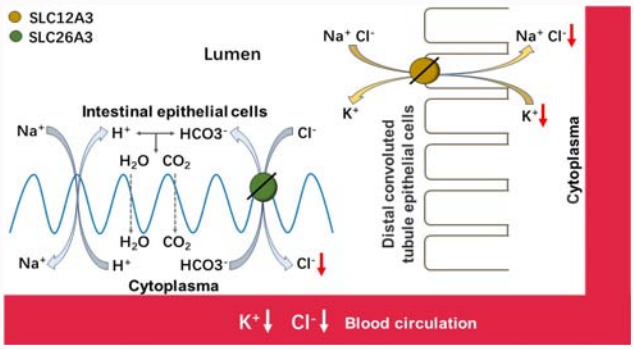

Figure 2: A schematic illustration to demonstrate Gitelman syndrome combined with congenital chloride losing diarrhea caused by *SLC12A3* and *SLC26A3* mutations.
This schematic illustration shows that the missense mutations in the SLC12A3 and SLC26A3 genes led to defective effects of their biological functions. Consequently, Na+ and Cl- reabsorption in the distal convoluted tubule of kidneys is decreased, while K+ excretion through urine is increased. At the same time, the intestinal electrolyte absorption of Cl- is reduced. Therefore, the clinical serum test shows that K+ and Cl- levels in blood circulation are significantly lower than the normal levels of healthy subjects.

in patients after 6 years old, while CCLD can be seen in childhood. Both diseases may strike anyone at any age and at any time [2-4,6-9]. In the current study, the patient was examined to know the lower potassium and chloride levels just after giving birth and suffering from amniotic fluid embolism and coma. Although we do not fully understand whether the postpartum amniotic fluid embolism and coma cause the onset of GS, it is certain that we have applied a molecular diagnostic approach to identify the mutations of the *SLC12A3* and *SLC26A3* genes and finally determined that this patient had not only GS but also CCLD. The combination of GS and CCLD in this patient is due to the heterozygous mutations D486N in SLC12A3 and S211T in SLC26A3. In addition, we found the heterozygous mutations in the *CFTR* and *CLDN16* genes in this patient (Table 3). To better understand the molecular mechanism of the disease caused by these two gene mutations, we have prepared a schematic diagram

Table 2: A list of the studied genes.

ABCB6	*AGT*	*AQP2*	*ATP1A1*	*ATP1A2*	*ATP1A3*	*ATP1B1*	*ATP1B2*	*ATP1B4*	*ATP6V0A4*
ATP6V1B1	*BSND*	*CA2*	*CACNA1D*	*CACNA1S*	*CASR*	*CFTR*	*CLCNKA*	*CLCNKB*	*CLDN16*
CLDN19	*CUL3*	*CYP11B1*	*CYP11B2*	*CYP17A1*	*EGF*	*FXYD1*	*FXYD2*	*HSD11B2*	*INVS*
KCNJ1	*KCNJ2*	*KCNJ5*	*KCNK7*	*KCNJ10*	*KCNJ18*	*KCNMA1*	*KCNMB1*	*KCNMB2*	*KCNMB3*
KCNMB4	*KCNT1*	*KCNT2*	*KCNU1*	*KLHL3*	*MAGED2*	*NR0B1*	*NR3C2*	*PCBD1*	*PIEZO1*
PRKCA	*REN*	*RYR1*	*SCN4A*	*SCNN1A*	*SCNN1B*	*SCNN1G*	*SLC12A1*	*SLC12A3*	*SLC26A3*
SLC4A1	*SLC4A4*	*KCNK13*	*KCNK12*	*TRPM6*	*WNK1*	*WNK4*			

ABCB6: ATP Binding Cassette Subfamily B Member 6; AGT: Angiotensinogen; AQP2: Aquaporin 2; ATP1A1: ATPase Na+/K+ Transporting Subunit Alpha 1; ATP1A2: ATPase Na+/K+ Transporting Subunit Alpha 2; ATP1A3: ATPase Na+/K+ Transporting Subunit Alpha 3; ATP1B1: ATPase Na+/K+ Transporting Subunit Beta 1; ATP1B2: ATPase Na+/K+ Transporting Subunit Beta 2; ATP1B4: ATPase Na+/K+ Transporting Subunit Beta 4; ATP6V0A4: ATPase H+ Transporting V0 Subunit A4; ATP6V1B1: ATPase H+ Transporting V1 Subunit B1; BSND: Barttin CLCNK Type Accessory Subunit Beta; CA2: Carbonic Anhydrase 2; CACNA1D: Calcium Voltage-Gated Channel Subunit Alpha1 D; CACNA1S: Calcium Voltage-Gated Channel Subunit Alpha1 S; CASR: Calcium Sensing Receptor; CFTR: CF Transmembrane Conductance Regulator; CLCNKA: Chloride Voltage-Gated Channel Ka; CLCNKB: Chloride Voltage-Gated Channel Kb; CLDN16: Claudin 16; CLDN19: Claudin 19; CUL3: Cullin 3; CYP11B1: Cytochrome P450 Family 11 Subfamily B Member 1; CYP11B2: Cytochrome P450 Family 11 Subfamily B Member 2; CYP17A1: Cytochrome P450 Family 17 Subfamily A Member 1; EGF: Epidermal Growth Factor; FXYD1: FXYD Domain Containing Ion Transport Regulator 1; FXYD2: FXYD Domain Containing Ion Transport Regulator 2; HSD11B2: Hydroxysteroid 11-Beta Dehydrogenase 2; INVS: Inversin; KCNJ1: Potassium Inwardly Rectifying Channel Subfamily J Member 1; KCNJ2: Potassium Inwardly Rectifying Channel Subfamily J Member 2; KCNJ5: Potassium Inwardly Rectifying Channel Subfamily J Member 5; KCNK7: Potassium Two Pore Domain Channel Subfamily K Member 7; KCNJ10: Potassium Inwardly Rectifying Channel Subfamily J Member 10; KCNJ18: Potassium Inwardly Rectifying Channel Subfamily J Member 18; KCNMA1: Potassium Calcium-Activated Channel Subfamily M Alpha 1; KCNMB1: Potassium Calcium-Activated Channel Subfamily M Regulatory Beta Subunit 1; KCNMB2: Potassium Calcium-Activated Channel Subfamily M Regulatory Beta Subunit 2; KCNMB3: Potassium Calcium-Activated Channel Subfamily M Regulatory Beta Subunit 3; KCNMB4: Potassium Calcium-Activated Channel Subfamily M Regulatory Beta Subunit 4; KCNT1: Potassium Sodium-Activated Channel Subfamily T Member 1; KCNT2: Potassium Sodium-Activated Channel Subfamily T Member 2; KCNU1; Potassium Calcium-Activated Channel Subfamily U Member 1 ; KLHL3: Kelch Like Family Member 3; MAGED2: MAGE Family Member D2; NR0B1: Nuclear Receptor Subfamily 0 Group B Member 1; NR3C2: Nuclear Receptor Subfamily 3 Group C Member 2; PCBD1: Pterin-4 Alpha-Carbinolamine Dehydratase 1; PIEZO1: Piezo Type Mechanosensitive Ion Channel Component 1; PRKCA: Protein Kinase C Alpha; REN: Renin; RYR1: Ryanodine Receptor 1; SCN4A: Sodium Voltage-Gated Channel Alpha Subunit 4; SCNN1A: Sodium Channel Epithelial 1 Subunit Alpha; SCNN1B: Sodium Channel Epithelial 1 Subunit Beta; SCNN1G: Sodium Channel Epithelial 1 Subunit Gamma; SLC12A1: Solute Carrier Family 12 Member 1; SLC12A3: Solute Carrier Family 12 Member 3; SLC26A3: Solute Carrier Family 26 Member 3; SLC4A1: Solute Carrier Family 4 Member 1; SLC4A4: Solute Carrier Family 4 Member 4; KCNK13: Potassium Two Pore Domain Channel Subfamily K Member 13; KCNK12: Potassium Two Pore Domain Channel Subfamily K Member 12; TRPM6: Transient Receptor Potential Cation Channel Subfamily Member 6; WNK1: WNK Lysine Deficient Protein Kinase 1; WNK4: WNK Lysine Deficient Protein Kinase 4

Table 3: Identification of the variants in *SLC12A3*, *SLC26A3*, *CFTR* and *CLDN16*.

Pathogenic gene	Full name	Genomic location*	Protein	Biological function	mRNA/Exon	Variant	Genotype	Pathogenicity Analysis	Clinical manifestation (Mode of inheritance)
SLC12A3	Solute Carrier Family 12 (Sodium/Chloride Transporter), Member 3	chr16:56,865,207-56,915,850	1021 AA 113139 Da	A renal thiazide-sensitive sodium-chloride cotransporter. It is highly expressed in the distal convoluted tubule of kidneys.	NM_000339 Exon 12	p.D486N c.1456G>A in exon 12	Het	Likely pathogenic	Gitelman syndrom (AR).
SLC26A3	Solute Carrier Family 26 (Anion Exchanger), Member 3	chr7:107,765,467-107,803,225	764 AA 84505 Da	A transmembrane glycoprotein that transports chloride ions across the cell membrane in exchange for bicarbonate ions. It is localized to the mucosa of the lower intestinal tract, particularly to the apical membrane of columnar epithelium and some goblet cells.	NM_999111 Exon 6	p.S211T c.632G>C in exon6	Het	Likely pathogenic	Congenital chloride losing diarrhea (AR)
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator	chr7:117,287,120-117,715,971	1480 AA 168142 Da	A member of the ATP-binding cassette transporter superfamily. It functions as a chloride channel, making it unique among members of this protein family, and controls ion and water secretion and absorption in epithelial tissues.	NM_000492 Exon 4	p.I160M c.480T>G	Het	Uncertain	1 Hereditary pancreatitis (AD) 2 Bronchiectasis with or without increased sweat chloride type 1 (AD) 3 Cystic fibrosis (AR)

CLDN16	Claudin 16	chr3:190,290,361-190,412,138	235 AA 26078 Da	A member of the claudin family, is an integral membrane protein and a component of tight junction strands. It is found primarily in the kidneys, specifically in the thick ascending limb of Henle, where it acts as either an intercellular pore or ion concentration sensor to regulate the paracellular resorption of magnesium ions.	NM_006580 Exon 3	p.I153T c.458T>C	Het	Uncertain	Renal and primary hypomagnesemia (AD)

AA: Amino Acids; AD: Autosomal Dominant; AR: Autosomal Recessive; Het: Heterozygous genotype. * Latest assembly from GRCh38/hg38.

in Figure 2. This figure represents that the *SLC12A3* gene mutation causes its dysfunction and subsequently results in a decrease in the recovery of Na^+, Cl^-, and K^+ in the distal convoluted tubules of kidneys, while the excretion of K through urine increases relatively [12]. The *SLC26A3* gene mutation leads to a decreased absorption of Cl^- and K^+ into blood circulation and an increase in fecal excretion [13-15]. Owning to defective *SLC12A3* and *SLC26A3*, a combination of GS and CCLD in the patient was finally observed in clinics.

Based on this case, we would like to summarize the diagnostic experience of clinical hypokalemia to reduce the misdiagnosis. For the patients with clinically encountered hypokalemia, we first assessed the severity of hypokalemia and performed arterial blood gas analysis to indicate whether there was metabolic alkalosis or acidosis, which might provide important evidence for the differential diagnosis of the causes of subsequent hypokalemia; We then performed the 24-h urinary potassium testing. Before potassium supplementation, both arterial blood gas analysis and 24-h urinary potassium excretion should be performed, otherwise, intravenous or oral potassium supplementation might interfere with the experimental results and affect diagnosis. Furthermore, we paid attention to the inquiry and improvement of medical history and medication history, such as whether it is accompanied by Sjogren's syndrome, hypertension, hyperthyroidism, or long-term use of diuretics. These syndromes could further indicate the cause of low potassium.

Conclusion

In conclusion, we have diagnosed the patient a 24-year-old Chinese woman with GS and CCLD owning to heterozygote variants of *SLC12A3* (p.D486N) and *SLC26A3* (p.S211T) by using a molecular diagnosis approach.

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