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Novel compound heterozygous mutation of *SLC12A3* in Gitelman syndrome co-existent with hyperthyroidism: A case report and literature review

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Abstract

BACKGROUND

Gitelman syndrome (GS) is a rare inherited autosomal recessive tubulopathy, characterized clinically by hypokalemia, hypomagnesemia, hypocalciuria, and metabolic alkalosis, and is caused by an inactivating mutation in *SLC12A3*. GS is prone to misdiagnosis when occurring simultaneously with hyperthyroidism. It is important to consider the possibility of other diseases when hyperthyroidism is combined with hypokalemia, which is difficult to correct.

CASE SUMMARY

A female patient with hyperthyroidism complicated with limb weakness was diagnosed with thyrotoxic hypokalemic periodic paralysis for 4 mo. However, the patient's serum potassium level remained low despite sufficient potassium replacement and remission of hyperthyroidism. GS was confirmed by whole exome and Sanger sequencing. Gene sequencing revealed compound heterozygous mutations of c.488C>T (p.Thr163Met), c.2612G>A (p.Arg871His), and c.1171_1178dupGCCACCAT (p.Ile393fs) in *SLC12A3*. Protein molecular modeling was performed to predict the effects of the identified missense mutations. All three mutations cause changes in protein structure and may result in abnormal protein function. All previously reported cases of GS coexisting with autoimmune thyroid disease are reviewed.

CONCLUSION

We have identified a novel compound heterozygous mutation in *SLC12A3*. The present study provides new genetic evidence for GS.

Key Words: *SLC12A3*; Gitelman syndrome; Hyperthyroidism; Hypokalemia; Gene sequencing; Case report

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Core Tip: In the present study, we report a patient with hyperthyroidism who was diagnosed with Gitelman syndrome (GS) through genome sequencing. We identified a novel compound heterozygous mutation in *SLC12A3*. Protein molecular modeling was performed to predict the effects of the identified missense mutations, which cause changes in protein structure and may result in abnormal protein function. All previously reported cases of GS coexisting with autoimmune thyroid disease are reviewed.

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INTRODUCTION

Gitelman syndrome (GS) is a rare, inherited, autosomal recessive, salt-losing tubulopathy, characterized clinically by hypokalemia, hypomagnesemia, hypocalciuria, and metabolic alkalosis. It is associated with an inactivating mutation in the *SLC12A3* (OMIM: 600968) gene, which is located on chromosome 16q13 and encodes the thiazide-sensitive sodium chloride cotransporter (NCCT)[1,2]. Thyrotoxic hypokalemic periodic paralysis (THPP) is characterized by recurrent episodic hypokalemia and muscle weakness, and is associated with hyperthyroidism[3]. GS occurring simultaneously with hyperthyroidism is prone to misdiagnosis. Here, we report the case of a young Chinese woman with hyperthyroidism complicated with GS caused by novel compound heterozygous variants of *SLC12A3*.

CASE PRESENTATION

Chief complaints

A 29-year-old woman was admitted to the Department of Endocrinology with a complaint of weakness in her lower limbs for 4 mo.

History of present illness

The patient had a nearly 1-year history of bilateral lower limb weakness. In August 2020, she was diagnosed with hyperthyroidism and THPP at a local hospital. The symptoms of her lower limb weakness were not relieved after 4 mo of antithyroid drug treatment and intermittent potassium supplementation. She presented to our hospital for evaluation in December 2020.

History of past illness

The patient had no history of long-term vomiting or diarrhea and did not use diuretics, laxatives, or glycyrrhizin.

Personal and family history

No history of genetic diseases in the family was reported.

Physical examination

The patient was 163.0 cm tall and weighed 49.0 kg (body mass index 18.4 kg/m²). She had grade I thyroid gland enlargement, and the muscle strength in her lower limbs was grade IV[4]. The limb muscle tone was normal and vital signs were as follows: Body temperature, 36.4 °C; pulse rate, 102 beats per minute; respiratory rate, 18 breaths per minute; and blood pressure, 112/78 mmHg.

Laboratory examinations

The biochemical parameters of the patient are shown in Table 1. Biochemical tests revealed hyperthyroidism [thyroid stimulating hormone < 0.005 μ U/mL, free triiodothyronine (FT3) 13.46 pmol/L, and FT4 37.15 pmol/L], and hypokalemia (serum potassium, 3.09 mmol/L). In addition, the patient had hypomagnesemia, hypocalciuria, metabolic alkalosis, and hyperreninemic hyperaldosteronism.

Based on the above inspection results, we suspected that the patient did not have THPP but GS or Bartter syndrome (BS). Because patients with GS or type III BS also have hypomagnesemia and hypocalciuria, and a minority of GS patients harbor mutations in the *CLCNKB* gene[5], further genetic counseling is needed to distinguish between these two possibilities.

Imaging examinations

Thyroid ultrasound showed diffuse thyromegaly with uniform echopattern. No abnormality was seen on X-ray chest film, abdominal ultrasound, and adrenal ultrasound.

Targeted sequencing

Whole blood samples were collected from the proband and her parents, son, and daughter. The patient had one elder brother, but we were unable to obtain a blood sample from him. We further examined for mutations in six genes (*SLC12A3*, *SLC12A1*, *KCNJ1*, *CLCNKA*, *CLCNKB*, and *BSND*) known to be associated with GS and BS using whole exome sequencing, and the suspected variations were verified by Sanger sequencing. Gene sequencing for all samples was performed at KingMed Diagnostics (Guangzhou, China).

Molecular structural analysis

To evaluate the effects of the three mutations in *SLC12A3*, protein molecular modeling was performed using SWISS-MODEL (<https://swissmodel.expasy.org/>) based on a template from the AlphaFold Protein Structure Database (<https://alphafold.ebi.ac.uk/>)[6,7]. PyMOL 1.7 was used for visualization and analysis of the three-dimensional protein structure. In addition, conservation analysis between species of the two missense mutations, T163M and R871H, was also implemented using ClustalW[8].

Novel genetic findings

As shown in Figures 1 and 2, the patient was found to have compound heterozygous mutations in *SLC12A3* [c.488C>T (p.Thr163Met) in exon 3, c.2612G>A (p.Arg871His) in exon 22, and c.1171_1178dupGCCACCAT (p.Ile393fs) in exon 9]. Her mother carried a heterozygous mutation, p.Ile393fs (Figure 2B), and her father carried two heterozygous mutations, p.Thr163Met and p.Arg871His (Figures 2A and 2C). Both p.Thr163Met and p.Arg871His missense mutations were inherited from her father, while the p.Ile393fs frameshift mutation was from her mother. These three mutations were passed on to the children. The variants c.488C>T and c.2612G>A have been described in the literature[9]. A new heterozygous frameshift duplication, c.1171_1178dupGCCACCAT, which has not been reported in the literature and databases (dbSNP, Clinvar, ExAC, and 1000 Genomes), was also identified. No variations were detected in the genes related to BS (data not shown).

Effects of the mutations on the protein structure of *SLC12A3*

The effects of the three mutations on *SLC12A3* structure were predicted. As shown in Figure 3, multiple sequence alignments focusing on mutation sites 163 and 871 show that these two loci are highly conserved in various species; thus, the replacements are more likely to cause disease (Figure 3A). Thr163 and Arg871 are located in two different protein domains (Figure 3B). Thr163 resides in an α -helix region and forms two hydrogen bonds with Leu159 and one hydrogen bond with Gly167. When mutated to Met, one of the hydrogen bonds that interacts with Leu159 was destroyed (Figures 3E and 3F). R871H showed a huge change in the hydrogen bond network. Arg871 forms several H-bonds with Ile840, Asp841, Ile842, and Tyr975. When positively charged Arg was replaced by neutral ring-containing His at location 871, the three original H-bond interactions with Asp841 and Tyr975 were missed, and one new H-bond interaction with Glu901 was generated (Figures 3G and 3H). Unlike the above two mutations, c.1171_1178dupGCCACCAT (p.Ile393fs) is a frameshift mutation that leads to a premature stop codon, because of which, some transmembrane regions and topological domains cannot be translated further (Figures 3C and 3D). Therefore, all three mutations were predicted to cause changes in the protein structure and may result in abnormal protein function.

FINAL DIAGNOSIS

According to the laboratory tests and genetic testing, the patient was finally diagnosed with GS concomitant with hyperthyroidism.

Table 1 Laboratory findings of the proband on admission

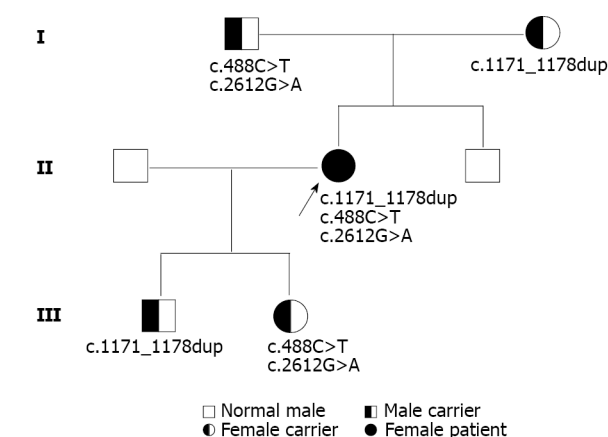
Characteristic	Detection value	Reference range	Characteristics	Detection value	Reference range
Age (yr)	29	-	Hormones		
Height (cm)	163.0	-	Thyroid stimulating hormone ($\mu\text{U/mL}$)	< 0.005	0.27-4.2
Weight (kg)	49.0	-	Free triiodothyronine (pmol/L)	13.46	3.1-6.8
Body mass index (kg/m^2)	18.4	-	Free tetraiodothyronine (pmol/L)	37.15	12-22
Blood pressure (mmHg)	112/78	-	Anti-thyroid peroxidase antibody (U/mL)	18.2	< 34
Biochemistry			Antithyroglobulin antibody (U/mL)	179.6	< 115
Total cholesterol (mmol/L)	4.23	< 5.20	Thyrotrophin receptor antibody (U/L)	2.8	0-1.75
Triglyceride (mmol/L)	1.32	< 1.70	Aldosterone (pg/mL), upright position	451.0	40-310
High-density lipoprotein (mmol/L)	0.89	1.04-1.55	Renin (pg/mL), upright position	454.0	4-38
Low-density lipoprotein (mmol/L)	2.12	< 3.40	Aldosterone (pg/mL), supine position	287	10-160
eGFR (mL/min/1.73 m^2)	120.3	-	Renin (pg/mL), supine position	206	4-24
Serum uric acid ($\mu\text{mol/L}$)	391.0	155-357	Parathyroid hormone (pg/mL)	34.1	15-65
Alanine transaminase (U/L)	13	7-40	Adrenocorticotrophic hormone (pg/mL)		
Aspartate aminotransferase (U/L)	17	13-35	8 am	15.76	1.6-13.9
Total bilirubin ($\mu\text{mol/L}$)	28.4	< 21.0	4 pm	12.35	-
Direct bilirubin ($\mu\text{mol/L}$)	8.6	< 8.0	0 am	5.02	-
Sodium (mmol/L)	137.0	137-147	Serum cortisol ($\mu\text{g/dL}$)		
Potassium (mmol/L)	3.09	3.5-5.3	8 am	12.03	6.02-18.4
Chloride (mmol/L)	94.5	99-110	4 pm	8.14	2.3-11.9
Calcium (mmol/L)	2.33	2.11-2.52	0 am	4.29	-
Magnesium (mmol/L)	0.60	0.65-1.25	Arterial blood gas analysis		
24-h urinary electrolytes			pH	7.49	7.35-7.45
Sodium (mmol/24 h)	127.60	137-257	pCO ₂ (mmHg)	40	35-45
Potassium (mmol/24 h)	67.98	36-90	pO ₂ (mmHg)	135	80-100
Chloride (mmol/24 h)	166.10	170-250	HCO ₃ ⁻ (mmol/L)	30.5	22-27
Calcium (mmol/24 h)	0.24	2.5-7.5	Base excess (mmol/L)	6.6	-2.3-2.3
Phosphate (mmol/24 h)	13.39	16.15-42	Potassium (mmol/L)	2.4	3.5-5.5
Urine volume (L/24 h)	1.10	-			

TREATMENT

Together with the antithyroid drug methimazole (10 mg/d), we administered spironolactone (40 mg/d), oral potassium chloride (3 g/d), and potassium magnesium aspartate (two tablets three times a day; each tablet contained 158 mg of potassium aspartate and 140 mg of magnesium aspartate). The doses of the above medicines were adjusted according to careful monitoring of thyroid functions as well as serum potassium and magnesium levels. The patient regained normal strength, and was discharged after 7 d.

OUTCOME AND FOLLOW-UP

Following discharge from the hospital, hypokalemia persisted for more than one year of follow-up



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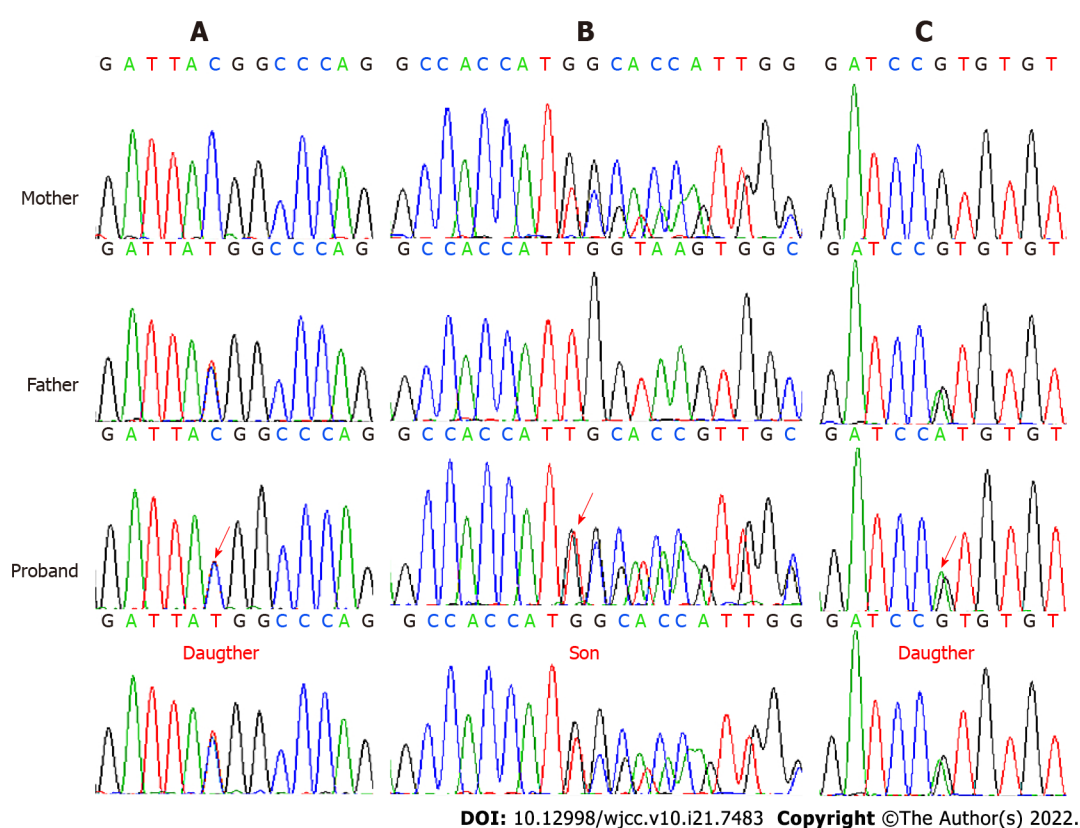
Figure 1 Pedigree diagram showing proband (arrow) and segregation of *SLC12A3*.

Figure 2 Sanger sequencing images of pedigree mutation type in *SLC12A3*. The sequence diagram from the first to the fourth row represents the mother, father, proband, and son or daughter, respectively. A: The NM_000339.2:c.488C>T(p.Thr163Met) (indicated by the red arrow) is a heterozygous missense mutation in exon 3; B: The NM_000339.2:c.1171_1178dupGCCACCAT(p.Ile393fs) (indicated by the red arrow) is a heterozygous frameshift mutation in exon 9; C: The NM_000339.2:c.2612G>A(p.Arg871His) (indicated by the red arrow) is a heterozygous missense mutation in exon 22.

despite remission of hyperthyroidism, and sufficient potassium and magnesium supplementation; however, limb weakness did not recur. The treatment and follow-up results for the thyroid functions and serum electrolyte levels are shown in Table 2 and Figure 4. According to the recommendations of the kidney disease: Improving Global Outcomes Controversies Conference, a reasonable target for serum potassium and magnesium may be 3.0 and 0.6 mmol/L, respectively[10]. Genetic diseases, such as GS, often require lifelong treatment. We attempted to treat the patient with eplerenone, which has higher selectivity than spironolactone for the aldosterone receptor. However, the patient could not tolerate the adverse effects of eplerenone because of low blood pressure and dizziness. The patient is still being followed at our department.

Table 2 Results of thyroid function tests on admission and follow-up

Date	FT3 (3.1-6.8 pmol/L)	FT4 (12-22 pmol/L)	TSH (0.27-4.2 μU/mL)	TGAb (< 115 U/mL)	TPOAb (< 34 U/mL)	TRAb (0-1.75 U/L)
October 2020	23.28	48.61	< 0.005	NA	NA	3.69
November 2020	23.46	37.15	< 0.005	179.6	18.2	2.80
31 December 2020	3.97	12.66	0.28	NA	NA	NA
09 February 2021	4.83	14.57	1.64	NA	NA	NA
26 April 2021	5.18	15.50	1.83	NA	NA	NA
23 July 2021	5.82	16.80	2.66	NA	NA	NA
15 December 2021	6.03	16.41	1.68	24.56	25.48	1.38

FT3: Free triiodothyronine; FT4: Free tetraiodothyronine; TSH: Thyroid stimulating hormone; TPOAb: Anti-thyroid peroxidase antibody; TGAb: Antithyroglobulin antibody; TRAb: Thyrotrophin receptor antibody; NA: Not available.

DISCUSSION

A clinical diagnosis of GS remains largely one of the exclusions, as many non-inherited conditions can mimic its presentation. GS is usually detected during adulthood but can also be found in children, as early as infancy[11,12]. It is characterized by a diversity of clinical manifestations and high phenotypic variability. A combination of sex, genetic heterogeneity, modified genes, compensatory mechanisms, environmental factors, and dietary habits might be involved in such variability[13]. Therefore, GS may easily be missed or misdiagnosed. In the present study, the case of hypokalemia in the young woman was initially diagnosed and treated as hyperthyroidism and was subsequently re-diagnosed as GS concomitant with hyperthyroidism, following genetic testing. Genetic testing revealed triple potential pathogenic variants in *SLC12A3* of combined heterozygosity. These mutations are expected to modify the protein structure and are implicated in NCCT dysfunction.

To date, more than 500 scattered mutations throughout *SLC12A3* have been reported in > 1300 patients with GS[10,14]. The prevalence of GS in the Caucasian population was found to be approximately 1 to 10 per 40000, and is potentially higher in Asia[10,15,16]. The estimated incidence rates of Graves' disease (GD) and Hashimoto's thyroiditis (HT) among the entire Chinese population are 120/100000/year and 100/100000/year, respectively[17]. Thus far, many case reports have shown GS and autoimmune thyroid disease (AITD) coexisting in a patient, suggesting that there may be a correlation between them. In our literature review, we found 22 case reports of patients with GS complicated with AITD, which are summarized in Table 3. All selected cases were genetically confirmed by sequencing. As shown in Table 3, the vast majority of cases described were compound heterozygous and were from Asian people. Among these patients with GS, 15 females (aged 18-56 years) and 8 males (aged 2-50 years) were included, 17 cases were complicated by GD, 4 had HT, 1 was diagnosed with subacute thyroiditis, and 1 was antibody-positive for AITD. It appears more likely that GS coexisted with GD compared with the other types of AITDs. THPP affects young Asian males more often than individuals of other ethnicities. A large genome-wide association study in southern China identified a susceptibility locus for THPP at 17q24.3, which could potentially affect the expression of *KCNJ2*, which is associated with hypokalemia[18]. Nevertheless, direct evidence for GS and THPP at the genetic level is not available.

NCCT, which is encoded by *SLC12A3* in the early distal convoluted tubules (DCT) of the kidney, facilitates the cotransport of sodium chloride from the pro-urine to the intracellular compartment. The reduced reabsorption of sodium and chloride ions due to the inactivation of NCCT leads to compensatory excessive exchange of Na⁺-K⁺ and Na⁺-H⁺ pumps, which eventually results in excessive excretion of potassium and hydrogen ions and hypokalemic alkalosis[19]. A huge loss of chloride ions in the DCT further enhances the polarity of DCT cells, which evokes an influx of extracellular calcium ions and hypocalciuria. Downregulation of the DCT epithelial magnesium ion channel transient receptor potential channel subfamily M, member 6 may be involved in the pathogenesis of hypomagnesemia accompanying NCCT inactivation[20]. In addition, low serum magnesium concentration may lead to rapid relapse of GD[21]. In contrast, thyroid morphology and function can be improved after magnesium supplementation[22]. With regard to thyroid disease, thyroid hormone directly participates in the regulation of the expression and/or activity of some ion channels and transporters, including Na⁺-K⁺-ATPase and Na⁺-H⁺ exchanger[23]. It is well established that excess triiodothyronine has an indirect effect through adrenergic stimulation, resulting in an increase in Na⁺-K⁺-ATPase pump activity[24]. The Na⁺-K⁺-ATPase pump activity in untreated patients with THPP is higher than that in other subjects with thyrotoxicity[25]. These may exacerbate the clinical features of GS. In the present case, the patient's clinical symptoms were relieved after comprehensive treatment including potassium and magnesium

Table 3 *SLC12A3* pathogenic variants identified in Gitelman syndrome complicated with thyroid disease to date

Case no.	Sex	Age	Serum potassium (mmol/L)	Serum magnesium (mmol/L)	Thyroid disease	Mutation type	DNA nucleotide change	Amino acid change	Ref.
1	F	29	3.09	0.60	GD	Compound heterozygote	c.488C>T	p.Thr163Met	This study
							c.2612G>A	p.Arg871His	This study
							c.1171_1178dupGCCACCAT	p.Ile393fs	This study
2	F	40	3.30	0.74	HT	Compound heterozygote	c.2552T>A	p.Leu849His	[37]
							c.2561G>A	p.Arg852His	
3	F	28	1.70	0.62	GD	Homozygote	c.2552T>A	p.Leu849His	[37]
4	F	18	3.20	0.86	GD	Compound heterozygote	c.1015A>C	p.Thr339Pro	[38]
							c.2573T>A	p.Leu858His	
5	F	50	3.00	0.66	GD	Compound heterozygote	c.539C>A	p.Thr180Lys	[38]
							c.1045C>T	p.Pro349Ser	
6	F	56	2.80	0.49	GD	Homozygote	c.1706C>T	p.Ala569Val	[38]
7	F	14	2.20	NA	GD	No mention	c.791G>C	p.Gly264Ala	[39]
8	M	16	2.27	0.40	GD	Compound heterozygote	c.1456G>A	p.Asp486Asn	[40]
							c.2102_2107delACAAGA	No mention	
9	F	42	3.20	0.50	HT	Compound heterozygote	c.248G>A	p.Arg83Gln	[41]
							NC_000016.10: g.56872655_56872667	No mention	
							(gcggacatttttg>accgaaaatttt)		
10	M	2	1.57	NA	GD	Compound heterozygote	c.1077C>G	p.Asn359Lys	[42]
							c.1567G>A	p.Ala523Thr	
11	M	45	2.11	0.54	GD	Homozygote	1562_1564delTCA	p.522delIle	[43]
12	M	21	2.10	NA	GD	Compound heterozygote	c.539C>A	p.Thr180Lys	[44]
							c.2573T>A	p.Leu858His	
13	M	35	1.80	NA	GD	Homozygote	c.1145C>T	p.Thr382Met	[45]
14	F	30	2.52	0.48	HT	Compound heterozygote	c.486_490delinsA	p.Thr163fs	[46]
							c.506-1G>A		
15	F	34	2.33	NA	HT	Compound heterozygote	c.953T>G	p.Phe318Cys	[47]
							c.1196G>A	p.Arg399His	
							c.1664C>T	p.Ser555Leu	
16	M	50	2.88	0.43	GD	Compound heterozygote	c.179C>T	p.Thr60Met	[48]
							c.1567G>A	p.Ala523Thr	
17	F	46	2.30	0.43	GD	Heterozygote	c.185C>T	p.Thr60Met	[49]
18	M	21	2.64	0.36	GD	Homozygote	c.2744G>A	p.Arg913Gln	[49]
19	F	50	2.66	0.62	GD	Compound heterozygote	c.179C>T	p.Thr60Met	[50]
							c.863T>G	p.Leu288Arg	
20	M	39	1.90	0.52	GD	Compound heterozygote	c.1841C>T	p.Ser614Phe	[51]
							c.2968G>A	p.Arg990Lys	
21	F	41	2.60	0.40	AP	Compound	c.964+2T>C		[51]

						heterozygote	c.179C>T	p.Thr60Met	
22	F	20	NA	NA	SAT	Compound heterozygote	c.1456G>A c.506-1G>A	p.Asp486Asn	[52]
23	F	47	NA	NA	GD	Compound heterozygote	c.1016C>T c.1925G>A	p.Thr339Ile p.Arg642His	[52]

GD: Graves' disease; HT: Hashimoto's thyroiditis; SAT: Subacute thyroiditis; AP: Antibody-positive; F: Female; M: Male; NA: Not available.

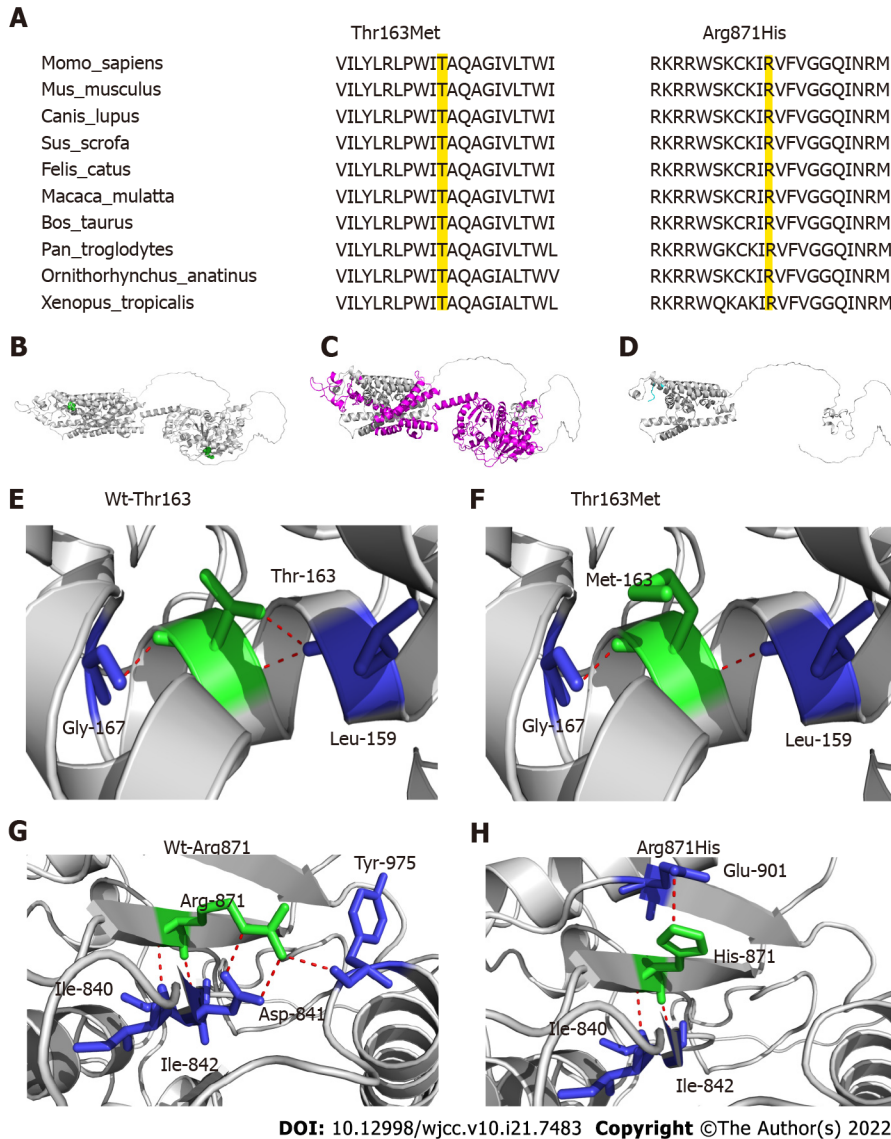


Figure 3 Schematic presentation of the structure of *SLC12A3*. A: Thr163 and Arg871 are highly conserved amino acids in various species (the locations colored yellow); B: Overview of the locations of Thr163 and Arg871 in the global three-dimensional structure of the protein. Thr163 and Arg871 are shown in green spheres, and the global protein structure is shown in the cartoon model; C and D: The mutation Ile393fs causes missing of some protein regions and domains (magenta), and transfer of MPPLAPAW* novel sequence (cyan); E and F: Analysis of changes in hydrogen bonds for the Thr163Met mutation. The key amino acids are shown as sticks and H-bonds are shown as red dotted line. One H-bond is destroyed when Thr163 is replaced by Met; G and H: The mutation Arg871His will cause large changes in the H-bond network, destruction of H-bond interaction with Asp841 and Tyr975, and generation of a new interaction with Glu901.

supplementation and improvement of thyroid function. Indeed, available evidence indicates that THPP results from a combination of genetics, thyrotoxicosis, and the environment[24]. *SLC12A3* is composed of 26 exons (> 130 kb). To date, all the identified mutations are widely distributed along 26 exons and some introns of *SLC12A3*. Combined heterozygosity with different mutations in each allele is the most frequent variant, with missense mutation being the most common type[26-28]. Notably, compound heterozygosity is a frequent occurrence in patients with GS coexisting with AITD (Table 3). In the

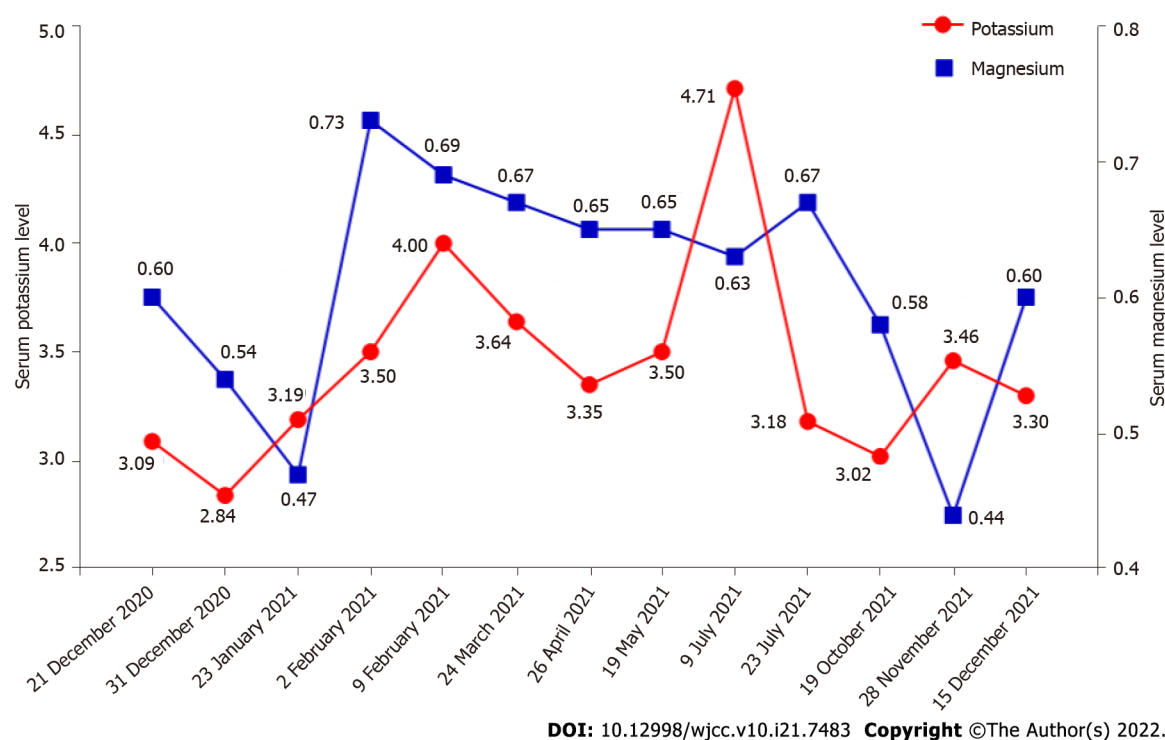


Figure 4 Hospital discharge follow-up results for serum electrolyte levels. The abscissa represents the date (format: Day/month/year). The double ordinates represent serum potassium level (the red line) and magnesium level (the blue line), respectively.

present case, triple mutations, including two missense mutations and one frameshift duplication, were identified. Triple mutations, with one mutation in one allele, have increasingly been reported in several studies[26,28,29]. Interestingly, the mutations p.Thr163Met and p.Arg871His are consistent with our findings on the same allele in unrelated Chinese-Taiwanese GS patients with triple mutations implying linkage disequilibrium, suggesting that there may be many hot spot mutations in *SLC12A3*[26] (Figure 2). In contrast, the recurrent mutations are very different in Japanese and European GS patients [30,31]. Screening these mutational hotspots will help us gain a better understanding of the genetic characteristics of GS in different ethnicities. However, GS was observed with a diversity of clinical manifestations ranging from being asymptomatic, fatigue, numbness, paresthesia, and neuromuscular weakness to paralysis or fatal arrhythmia[32-34]. Because direct sequencing does not necessarily cover large genomic rearrangements, a small number of false-negative genetic cases may be included in unsolved cases. Although much research has already been conducted, the association between phenotype and genotype in *SLC12A3* remains obscure. Here, we summarize representative studies in different ethnic groups. Among these constructive studies, GS genotypes caused by splicing, frameshift, and missense mutations are prone to a more severe phenotype than the other genotypes, whereas GS patients with two or more mutations may also present with more severe clinical manifestations[29,31,35, 36]. Additionally, male patients with GS have an earlier age of onset and more severe hypokalemia, suggesting that gender is an important factor[36]. Defining an association between phenotype and genotype is practically challenging. However, further research is needed to clarify this relationship. This study has some limitations. First, the research is limited to published studies that may miss some of the gray and/or non-English language literature. Second, only those GS patients who were confirmed by genetic testing were included in this study.

CONCLUSION

We have identified a novel compound heterozygous mutation in *SLC12A3*. It is important to consider other diseases when hyperthyroidism is combined with persistent hypokalemia. The present study provides new genetic evidence for GS.

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