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CASE REPORT

A novel homozygous *SLC12A3* mutation causing Gitelman syndrome with co-existent autoimmune thyroiditis: a case report and review of the literature

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Abstract
Gitelman syndrome is a rare, autosomal recessively inherited tubulopathy manifesting with hypokalemia, hypomagnesemia, hypocalciuria, and metabolic alkalosis. Common symptoms include fatigue, myalgia, reduced performance capacity, tetany, paresthesia, and delayed growth. However, as reported in the literature, diagnosis in some patients is prompted by an incidental finding of hypokalemia. GS develops due to mutations in the *SLC12A3* gene, which encodes the thiazide-sensitive Na-Cl cotransporter. Many variants in the *SLC12A3* gene causing GS have been reported in literature. A new pathogenic homozygous mutation (c.2612G > T), absence of hypomagnesemia, and accompanying autoimmune thyroiditis are remarkable in our patient. There are a few Gitelman syndrome cases that are complicated with autoimmune thyroiditis in the literature. In this study, we present a case of Gitelman syndrome with a novel homozygous mutation and accompanying autoimmune thyroiditis and review of the literature.

Keywords Gitelman syndrome · Autoimmune thyroiditis · A novel mutation · SLC12A3 · Hypokalemia · Hypomagnesemia

Abbreviations

GS	Gitelman syndrome
BS	Bartter syndrome
NCC	Na-Cl cotransporter
CKD	Chronic kidney disease

Introduction

Gitelman syndrome (GS) is a rare, autosomal recessively inherited tubulopathy manifesting with hypokalemia, hypomagnesemia, hypocalciuria, and metabolic alkalosis [1]. Studies have reported a prevalence of approximately 1/40,000 in Caucasians, and a higher prevalence in Asia [2]. GS generally affects adolescents and adults, whereas symptoms rarely appear during the neonatal period and childhood. Common symptoms include muscle weakness, fatigue, reduced performance capacity, fainting episodes, cramps, tetany, paresthesia, carpopedal spasm, delayed growth and puberty, short stature, thirst, vertigo, polyuria, joint pain, and vision problems. However, as reported in the literature, diagnosis in some patients is prompted by incidental detection of hypokalemia. Unlike Bartter syndrome (BS) which is often considered in the differential diagnosis, GS is accompanied by hypocalciuria, generally has a milder course and is diagnosed at a later age. However, it is not always easy to discriminate GS from Bartter syndrome type 3, in which mutations in the *CLCNKB* gene are observed in terms of clinical and laboratory features. Definitive discrimination, however, can be achieved using genetic tests.

GS is caused by mutations in the *SLC12A3* gene, which encodes the thiazide-sensitive Na-Cl cotransporter. Many variants of the *SLC12A*3 gene causing GS and autoimmune thyroid diseases accompanying cases with different genotypes have been reported in the literature [3–19]. However, reflection of these different pathogenic variants in the clinical phenotype remains unclear. In this study, we present a

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case of concomitant GS and autoimmune thyroiditis with novel variant and an extensive literature review.

Case report

A 32-year-old female patient applied to the outpatient clinic with a 1-year history of fatigue. Systemic inquiry revealed no remarkable features and physical examination was normal. There was no diarrhea, nausea, or vomiting. The patient's mother and father had a third-degree consanguineous marriage.

Hypokalemic alkalosis was detected in laboratory investigations. Consistent with renal potassium excretion, increased transtubular potassium gradient (10), hypocalciuria (72.8 mg/day), and increased chloride fractional excretion (1493 mmol/day) and plasma renin activity were observed. Spot urinary calcium/creatinine ratio was 0.05 and 0.09 (< 0.15) (Table 1). Hypomagnesemia was absent. Urea, creatinine, and 24 h creatinine clearance in the urine were in the normal range according to age and weight (Table 1). There was no use of diuretics, laxatives or any other medications, and no history of vitamin B_{12} replacement therapy. There was no history of use of alcohol or herbal product(s). She was normotensive according to 24 h ambulatory blood pressure monitoring (24 h average blood pressure, 117/72 mmHg). Aldosterone level was normal, plasma renin activity was increased, and cortisol was suppressed in the 1 mg dexamethasone test (Table 1). Abdomen MRI revealed normal renal parenchymal thickness, contour, and size.

Table 1 Laboratory findings

Parameter	Result	Reference range
Creatinine	0.52 mg/dL	0.5–0.9
Na	139 mmol/L	136–145
Cl	92 mmol/L	98–107
K	2.9 mmol/L	3.5–5.1
Ca	9.9 mg/dL	8.4–10.2
P	4.3 mg/dL	2.5–4.5
Mg	2.01 mg/dL	1.6–2.6
pH/HCO_3	7.47/ 30.7 mmol/L	7.35–7.45/22–26
1 mg DST[a]	0.48 µg/dl	< 1.8
Aldosterone	16.6 ng/dL	4–31
PRA[b]	10.5 ng/mL/h	< 5.7
TSH	7.04 mIU/L	0.27–4.2
fT_3[c]/fT_4[d]	4.06 ng/L/1.09 ng/dL	2–4.4/0.9–1.7
Anti-TPO[e]	290 IU/mL	0–34
Anti-TG[f]	644 IU/mL	0–115
Creatinine clearance	143 mL/min, 135 mL/min	90–150
24 h urine Na	201 mmol/day, 270 mmol/day	40–220
24 h urine K	94.6 mmol/day, 98.1 mmol/day	25–125
24 h urine Ca	72.8 mg/day, 91.2 mg/day	100–300
24 h urine Cl	1493 mmol/day, 233 mmol/day	110–250
24 h urine protein	252 mg/day, 244 mg/day	< 150
Spot urine Ca/Cr ratio[g]	0.05, 0.09	> 0.15
Urine potassium	33.8 mmol/L	20–80
Serum osmolality	295 mmol/kg	285–295
Urine osmolality	330 mmol/kg	50–1200
Transtubular potassium gradient	10	In hypokalemia, < 3

24-h urinalysis was studied twice

[a]1 mg dexamethasone suppression test

[b]Plasma renin activity

[c]Free triiodothyronine

[d]Free thyroxine

[e]Anti-thyroid peroxidase antibody

[f]Anti-thyroglobulin antibody

[g]Spot urine calcium creatinine ratio

GS was primarily considered in this hypokalemic normotensive patient with metabolic alkalosis who had renal potassium loss, hypocalciuria, increased renin activity, and increased chloride fractional excretion. Normal serum potassium levels could be maintained with oral potassium supplements (40 mEq/day). A tubulopathy screening panel was requested. Next-generation sequencing analysis revealed a homozygous c.2612G > T (p.Arg871Leu) variant in the *SLC12A3* (NM_000339.3) gene. Laboratory investigations further revealed subclinical hypothyroidism, with anti-thyroid peroxidase and anti-thyroglobulin autoantibody positivity and the patient was also diagnosed with Hashimoto's thyroiditis (Table 1).

Whole exome sequencing

The concentration and quality of genomic DNA (gDNA) extracted from peripheral blood were examined with the Qubit™ dsDNA BR Assay Kit (Thermo Scientific, USA). For WES analysis, 3 µg of genomic DNA (gDNA) was sheared to yield 100–450 bp fragments. Insolution whole-exome capture, circularization, and high-throughput sequencing were performed using the Twist Human Core Exome EF Multiplex Complete Kit (Twist Bioscience, South San Francisco), MGIEasy Circularization Kit (MGI, China), and DNBSEQ-G400RS High-throughput Sequencing Kit (FCL PE100) (MGI, China), respectively. Enriched DNA fragments were sequenced on the DNBSEQ-G400 platform as paired-end 100–125 base-pair reads. Total number of reads in target was 301 million, the mean coverage was 100 and the sequencing depth of the regions was 129.11. Targeted panel data analysis identified 15,691 variants. Among these variants with an effect on coding/splice site regions, the variant filtering strategy was based on allele frequency with MAF ≤ 1% variants and according to the phenotypic and clinic findings by Human Phenotype Ontology. The variants found were checked with the IGV (Integrative Genomics Viewer) program. The variants were extracted from candidate genes with the annotations of frameshift, stop gained, splice acceptor, splice donor, missense, and splice site region (within the terminal 1–5 bases of the exon or terminal 3–8 bases of the intron). Next-generation sequencing analysis revealed a novel homozygous c.2612G > T (p.Arg871Leu) variant in the *SLC12A3* (NM_000339.3) gene (shown in Fig. 1). The variant affects hotspot regions of the gene (PM1) and in silico tools evaluation results were compatible with the high pathogenicity scores (PP3) (shown in Figs. 2, 3). Previously, different pathogenic alteration was reported in same amino acid (PM5). The variant was not previously reported in gnomAD, 1000 genomes and ESP 6500 (PM2). The c.2612G > T variant was also detected in both father

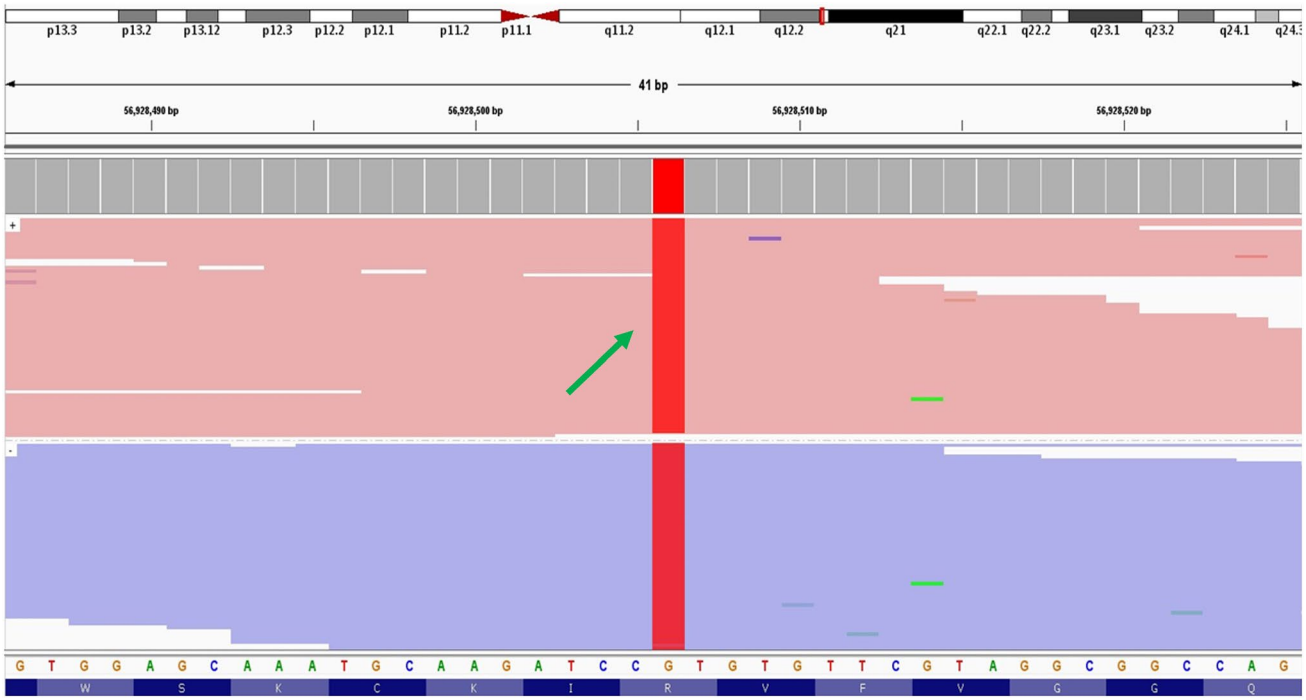

Fig. 1 Next generation sequencing (NGS) analysis indicates the homozygous c.2612G > T (p.Arg871Leu) variant in the *SLC12A3* gene in our patient (green arrow). Integrative genome browser (IGV) were conducted for variant visualization. The strands ordered and colored by read strands. While the pink color shows the forward reading strand (read 1), the light blue color indicates the reverse reading strand (read 2)

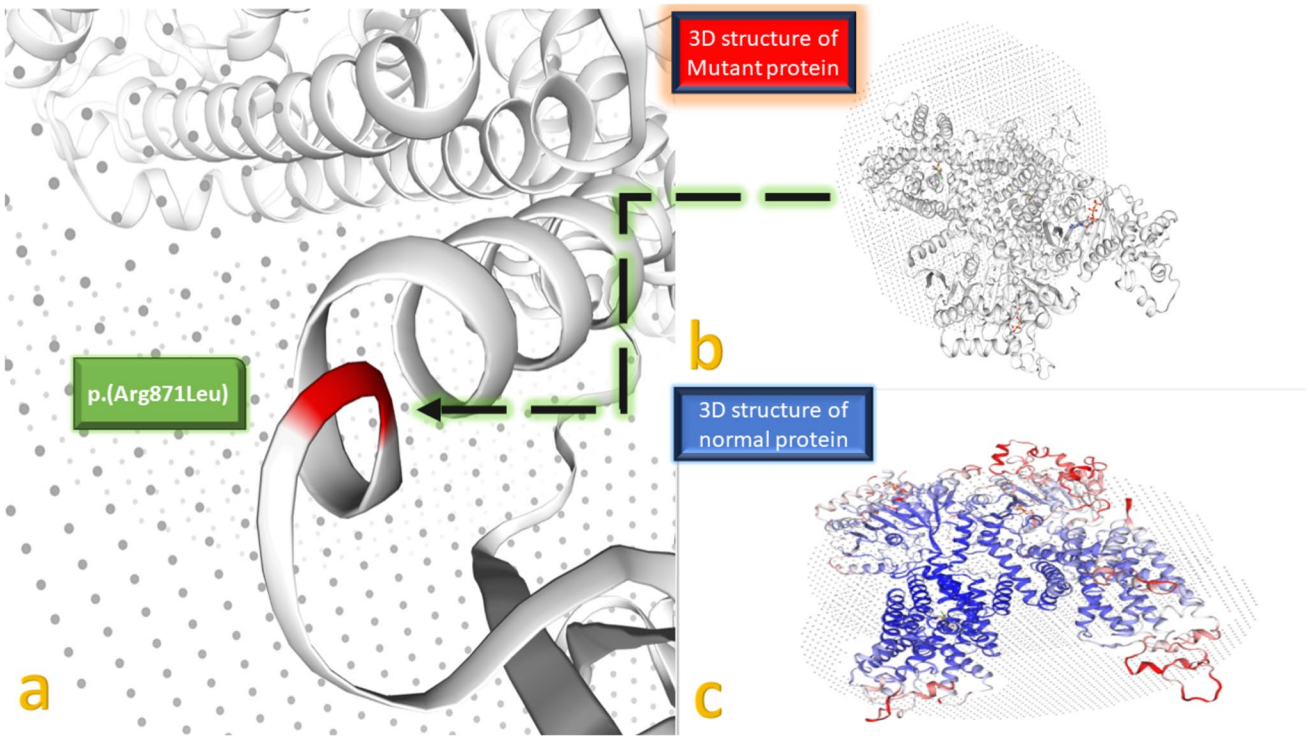

Fig. 2 S12A3_HUMAN(P55017) 3D protein structure modelling. **a** The c.2612G > T (p.Arg871Leu) alteration affects alpha-helix structure (arrow). **b** Mutant protein prediction. **c** Normal protein prediction. Swissmodel and alphafold was used to predict protein structure. DNA and protein sequence was taken from Ensembl and RCSB Protein Data Bank

and mother in heterozygous state. Therefore, the variation in our patient evaluated as a pathogenic according to ACMG guidelines (PM1, PM2, PM5, PP3) [20].

Discussion

To date, more than 50 hereditary tubulopathy syndromes have been reported [21]. GS is the most common salt-losing tubulopathy syndrome caused by mutations in the *SLC12A3* gene encoding for the thiazide-sensitive Na-Cl cotransporter [22]. When GS is suspected in a patient, it is recommended that a next-generation sequencing panel is performed. The genes in these panels should include *SLC12A3, CLCNKB,* and *HNF1B*. We initially requested a next-generation sequencing-based tubulopathy panel (Table 2).

To our knowledge, the homozygous c.2612G > T (p.Arg871Leu) variation detected in the *SLC12A3* (NM_00339.3) gene in our case has not been reported in the literature. Because the pathogenicity score was high and consistent with the clinical evaluation, it was considered to be a novel pathogenic variant. Additionally, the presence of an autoimmune thyroiditis i.e., (Hashimoto's thyroiditis) diagnosed along with GS was remarkable. There are a few reported cases of concomitant autoimmune thyroiditis and GS in the literature (Table 3) [3–19]. Nevertheless, studies have not been able to establish an association between autoimmune thyroid disease and GS.

A literature review revealed 23 cases of GS in total, including ours, that reported a *SLC12A3* gene mutation and accompanying autoimmune thyroid disease. Apart from our case, there were two patients diagnosed with Hashimoto's thyroiditis among the cases harboring a *SLC12A3* mutation. Including our case, 17 of 23 patients described in the literature had Graves' disease, three had Hashimoto's thyroiditis, and two had antibody-positive autoimmune thyroid disease (Table 3). Because thyrotoxicosis contributes to the deterioration of hypokalemia in patients diagnosed with Graves' disease, it is possible that these patients were diagnosed with GS, more commonly, by presenting with hypokalemia. When patients with GS accompanying Graves' disease are reviewed, the fact that some present with thyrotoxic hypokalemic paralysis supports this finding [7, 11, 19]. It is not known whether Hashimoto's thyroiditis in three cases was related to a genotype or was coincidental because Hashimoto's thyroiditis is already a common disorder in the population. Also a definitive association between Graves' disease and GS has not been demonstrated yet but there is some weak evidence reveals that some variants in *SLC12A3* coexist with autoimmune thyroiditis. Previously,

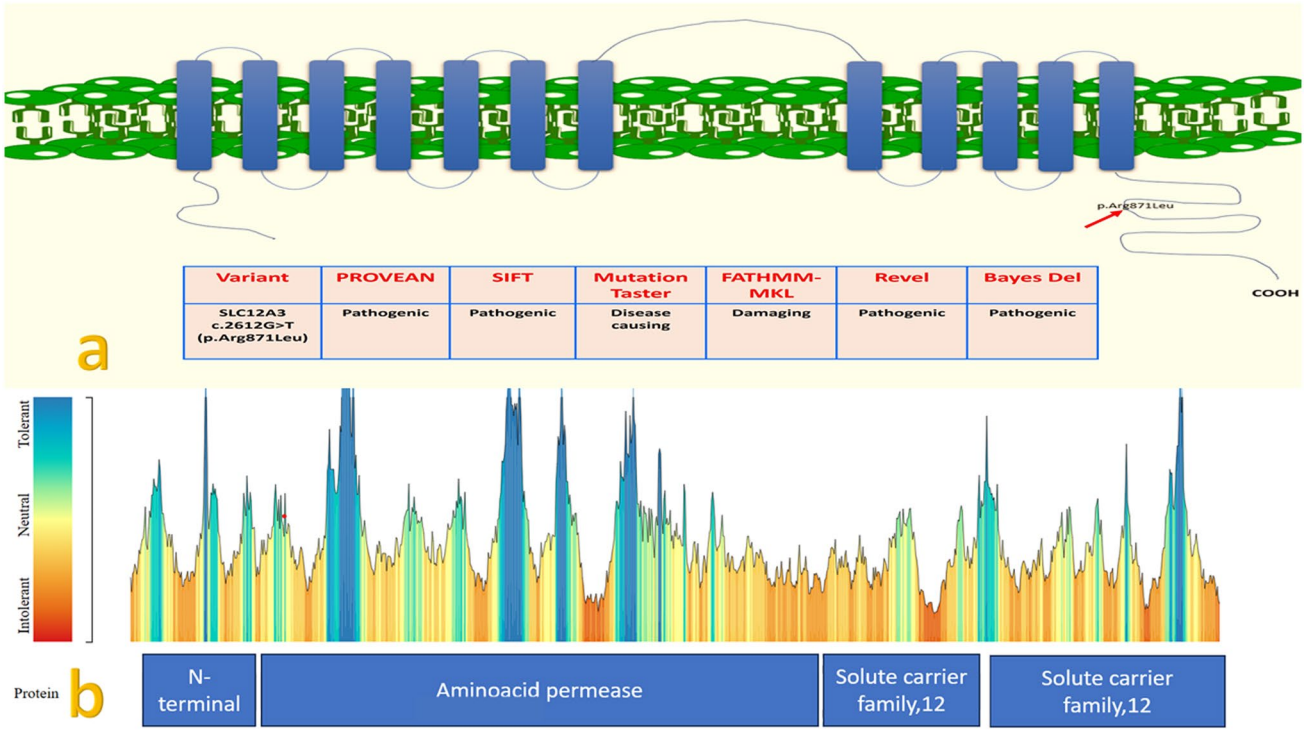

Fig. 3 **a** S12A3_HUMAN(P55017) protein cellular location and in silico tool predictions. A protein on the cell membrane is responsible for mediating Na/Cl transport. Our variant affects the C-terminus of the protein (red arrow). **b** SLC12A3 variant pathogenicity prediction and domain distribution. According to metadome, it consists of 4 functional domains. Solute carrier family 12 domain was affected by aminoacid alterations. The domain aminoacid prediction indicated that c.2612G > T (p.Arg871Leu) variants lead to slightly intolerant (ps/pi: 0.67) impact on protein structure

Table 2 Renal tubular disorders panel

SLC12A1	KCNJ1	BSND	CLCNKA	CRB2
SLC12A3	CLCNKB	MAGED2	CTNS	PAX2
CLCN5	CLCN1	OCRL	ATP6V0A4	TRPC6
ATP6V1B1	SLC4A1	CA2	CLDN19	INF2
CLDN16	CNNM2	EGF	FXYD2	MYO1E
RET	WNT11	GDNF	WT1	ACTN4
EYA1	PAX2	CD2AP	ANLN	APOL1
COL4A3	COL4A4	COL4A5	MYH9	SCNN1B
SCNN1G	CASR	GNA11	AP2S1	

some studies reported that there could be some relationship between clinical presentation and genotype of GS [23–25]. Some mutations (p.(T60M)) may be associated with earlier manifestation and lower calciuria [24], some (intronic or nonframeshift mutations) may be associated with severe hypokalemia [25].

The absence of hypomagnesemia can be considered to be due to the genotype. In a review published in 2019, 185 patients with GS in Japan were studied in terms of clinical and genetic characteristics, and that review revealed that patients with some genotypes have milder hypomagnesemia [26]. It has been reported that patients with c.2573T > A (p.Leu858His) and/or c.1924C > T (p.Arg642Cys) pathogenic variants, more commonly observed in the Japanese population, exhibit higher serum magnesium levels compared to those without these variants (1.76 mg/dL versus 1.43 mg/dL; $p < 0.001$). Apart from our case, there were only four cases (Case 1, 9, 10, 14) with normal magnesium levels and two of these cases (Case 9 and 14) had heterozygous c.2573T > A (p.Leu858His) pathogenic variants. Case 9 and 14 were the only cases that had c.2573T > A (p.Leu858His) pathogenic variant in the review and there was no case that had c.1924C > T (p.Arg642Cys) pathogenic variant. The homozygous c.2612G > T (p.Arg871Leu) variant in our case, which to our knowledge is reported here for the first time, can also be related to normal magnesium levels in our patient.

In our case, Arginine (Arg) at the 871st position was the aminoacid that changed (to Leucine). There are various reports documenting mutations at the 871st Arg position that cause different aminoacids [18, 27–30]. In an article examining DNA samples of 163 patients with a suspicion of GS, 114 different mutations were identified, 31 of which have not been reported before [27]. There is a case (out of 163 cases) that reported an aminoacid change of p.Arg871Cys

Table 3 Case reports with Gitelman syndrome manifesting *SLC12A3* mutation and diagnosed with autoimmune thyroiditis

No	Author	Year	Sex	Age	Thyroid disease	Tsh	fT3	fT4	Anti-TPO	Anti-TG	TRAB	Serum potassium (mmol/L)	Serum magnesium (mg/dL)	Mutation type	Variation site	Nucleotide change	Aminoacid change
1	Aoi et al. [3]	2007	F	40	AP	**N**	**N**	**N**	↑	NA	NA	3.3	1.8	Compound heterozygote	Exon 22 Exon 22	c.2552T > A, c.2561G > A	Leu849His Arg852His
2	Aoi et al. [3]	2007	F	28	GD	↓	↑	↑	NA	NA	↑	1.7	1.5	Homozygote	Exon 22	c.2552T > A	Leu849His
3	Dong et al. [4]	2010	M	39	GD	↓	↑	↑	NA	NA	↑	1.9	1.26	Compound heterozygote	Exon 15 Exon 26	c.1841C > T, c.2968G > A	Ser614Phe Arg990Lys
4	Dong et al. [4]	2010	F	41	AP	**N**	**N**	**N**	↑	NA	NA	2.6	0.97	Compound heterozygote	Intron 7 Exon 1	c.964 + 2T > C, c.179C > T	Thr60Met
5	Xu et al.[5]	2013	F	46	GD	↓	↑	↑	↑	NA	↑	2.3	1.04	Heterozygote	Exon 1	c.185C > T	Thr60Met
6	Xu et al.[5]	2013	M	21	GD	↓	↑	↑	↑	NA	↑	2.64	0.87	Homozygote	Exon 23	c.2744G > A	Arg913Gln
7	Zha et al. [6]	2015	F	14	GD	↓	↑	↑	↑	**N**	↑	2.2	1.29	NA	Exon 6	c.791G > C	Gly264Ala
8	Baldane et al.[7]	2015	F	35	GD		↑	↑	↑	↑	↑	1.8	NA	Homozygote	Exon 9	c.1145C > T	Thr382Met
9	Mizokami et al.[8]	2016	F	18	GD	↓	NA	↑	NA	NA	↑	3.2	2.09	Compound heterozygote	Exon 12 Exon 22	c.1015A > C, c.2573T > A	Thr339Pro Leu858His
10	Mizokami et al.[8]	2016	F	50	GD	↓	NA	↑	NA	NA	↑	3.0	1.6	Compound heterozygote	Exon 4 Exon 8	c.539C > A, c.1045C > T	Thr180Lys Pro349Ser
11	Mizokami et al.[8]	2016	F	56	GD	↓	NA	↑	NA	NA	↑	2.8	1.19	Homozygote	Exon 14	c.1706C > T	Ala569Val
12	Zhou et al. [9]	2018	M	45	GD	↓	↑	↑	↑	**N**	↑	1.4	1.31	Homozygote	Exon 12	c.1562-1564delTCA	522delIle
13	Liu et al. [10]	2018	M	16	GD	↓	↑	↑	↑	↑	↑	2.27	0.97	Compound heterozygote	Exon 12 Exon 17	c.1456G > A, c.2102-2107delACAAGA	Asp486Asn 701–702 delAsnLys
14	Oba et al. [11]	2019	M	21	GD	↓	↑	↑	NA	NA	↑	2.1	1.8	Compound heterozygote	Exon 4 Exon 22	c.539C > G, c.2573T > A	Thr180Lys Leu858His
15	Que et al. [12]	2020	F	30	HT	NA	NA	NA	NA	NA	NA	2.52	1.17	Compound heterozygote	NA NA	c.486-490delinsA, c.506-1G > A	Thr163fs

Table 3 (continued)

No	Author	Year	Sex	Age	Thyroid disease	Tsh	fT3	fT4	Anti-TPO	Anti-TG	TRAB	Serum potassium (mmol/L)	Serum magnesium (mg/dL)	Mutation type	Variation site	Nucleotide change	Aminoacid change
16	Peng et al. [13]	2020	M	50	GD	↓	↑	↑	**N**	**N**	↑	2.88	1.04	Compound heterozygote	NA	c.179C > T, c.1567G > A	Thr60Met Ala523Thr
17	Wang et al. [14]	2020	F	50	GD	NA	NA	NA	NA	NA	NA	2.66	1.51	Compound heterozygote	NA	c.179C > T, c.863T > G	Thr60Met Leu288Arg
18	Song et al. [15]	2021	F	47	GD	NA	NA	NA	NA	NA	NA	NA	NA	Compound heterozygote	NA	c.1016C > T, c.1925G > A	Thr339Ile Arg642His
19	Yu et al. [16]	2021	M	2	GD	NA	NA	NA	NA	NA	↑	NA	NA	Compound heterozygote	NA	c.1077C > G, c.1567G > A	Asn359Lys Ala523Thr
20	Zhang et al. [17]	2021	F	42	HT	↑	**N**	**N**	↑	↑	NA	3.2	1.22	Compound heterozygote	Exon 1 Exon 8	c.248G > A, g.56872655_56872667 (gcgga-catttttg > accgaaaatttt)	Arg83Gln Frameshift/ splice site mutation
21	Qin et al. [18]	2022	F	29	GD	↓	↑	↑	**N**	↑	↑	3.09	1.46	Compound heterozygote	Exon 3 Exon 9 Exon 22	c.488C > T, 1171-1178dupGCC ACCAT, c.2612G > A	Thr163Met Ile393fs Arg871His
22	Xu et al. [19]	2023	F	14	GD	↓	↑	↑	↑	**N**	↑	2.4	1.36	Compound heterozygote	Intron 3 Exon 12	c.506-1G > A, c.1456G > A	Splicing mutation Asp486Asn
23	Present case	2023	F	32	HT	↑	**N**	**N**	↑	↑	NA	2.9	2.01	Homozygote	Exon 22	c.2612G > T	Arg871Leu

In the literature, autoimmune thyroiditis was reported in seven more cases diagnosed with GS pathologically and biochemically with no *SLC12A3* mutation; however, patients with no genetic diagnosis were not included in Table 3

F female, *M* male, *GD* Graves' disease, *HT* Hashimoto's thyroiditis, *AP* antibody-positive, *NA* not available

(c.2611C > T) but no additional information was included about the phenotype [27].

In another article examined 20 patients with hypokalemia (16 patients with GS, 4 patients with BS), 12 NCC mutations, including six novel mutations were identified and one of the novel heterozygous mutations was p.Arg871His [28]. The patient with p.Arg871His variant had hypokalemia and hypomagnesemia at the presentation, unlike our patient. Like our patient, he was also admitted in early adulthood (age 28). His symptomatology at the presentation was paralysis, muscle weakness, cramps, nocturia, palpitation, and paresthesias; our patient did not have that rich symptomatology. Thyroiditis was not reported in that case [28].

p.Arg871His variant has been reported in three other articles [18, 29, 30]. In a study to understand the role of deep intronic mutations on GS with uniallelic or undetectable *SLC12A3* mutations, 29 patients with GS were evaluated and besides the deep intronic mutations, one patient with p.Arg871His variant was detected [29]. The patient had hypokalemia and hypomagnesemia and age at diagnosis in early adulthood (age 32), thyroiditis was not reported.

A larger study from Taiwan was performed on 117 Taiwanese GS patients to evaluate the genotype and phenotype correlation [30]. In this study, 40 different SLC12A3 mutations were identified and the authors concluded that patients with homozygous and deep mutations in intron 13 had more severe phenotypes. On the follow-up, out of 117 patients, 7 patients developed stage III or IV chronic kidney disease (CKD), 6 of the patients with CKD underwent renal biopsy, and revealed chronic tubulointerstitial nephritis in favor of hypokalemic nephropathy. The average age of CKD was 37 ± 3. In this GS patients with CKD, three patients were found to have Arg871His variant heterozygously. The age of disease onset was 15, 18, and 12 and the age of CKD were 38, 37, and 36 in patients with Arg871His variant. All three patients are male and had hypokalemia and hypomagnesemia, thyroiditis was not mentioned [30]. In this study, 42% (3/7) of patients with GS and CKD were shown to have one heterozygous p.Arg871His variant is also remarkable.

Another case with p.Arg871His variant is included in Table 3 because of the coexistence of autoimmune thyroiditis in the patient [18]. The patient with heterozygous p.Arg871His variant in this report had hypomagnesemia, unlike our patient; like our patient, she was admitted in early adulthood (age 29), and her symptom of presentation was bilateral lower limb weakness. Like our patient, she was diagnosed with autoimmune thyroiditis (Graves' disease) [18].

Also, a literature review was performed on the genotype of autoimmune thyroiditis, there were a limited number of cases with autoimmune thyroiditis examined by WES [31–33]. In a recent original article that performed exome sequencing to understand the genetic susceptibility to the coexistence of Hashimoto's thyroiditis and PCOS; 142 patients had Hashimoto's thyroiditis performed WES and SLC12A3 mutation was not reported [31]. In another article, four patients with Hashimoto's thyroiditis (four members of a family) were selected for WES and they found a missense mutation in PTPN22; a variant is not reported in the *SLC12A3* gene [32]. A family with an autosomal dominant inheritance of Hashimoto thyroiditis is also described in the literature and proband's WES identified a splice site variant in the thyroglobulin gene; the SLC12A3 variant was not reported in this case either [33].

In conclusion, GS should be suspected in adult patients with hypokalemia. Different genotypes have been reported in the *SLC12A3* gene causing GS. The homozygous variant detected in our case is a new pathogenic variant and accompanying autoimmune thyroiditis and the absence of hypomagnesemia should be underlined with this variant. It may be appropriate to screen patients for autoimmune thyroiditis who are diagnosed with GS in adulthood. Further studies are needed to characterize the relationship between different genotypes and clinical features in patients with GS.

Declarations

Conflict of interest The authors have declared that no conflict of interest exists.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Written informed consent was obtained from the patient for the publication of her clinical data.

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