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## Novel heterozygous missense mutation of *SLC12A3* gene in Gitelman syndrome: A case report

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### Abstract

#### BACKGROUND

To screen for possible pathogenic loci in a patient with Gitelman syndrome by high-throughput exome sequencing and to explore the relationship between genotype and phenotype.

#### CASE SUMMARY

The clinical data of the patient were collected. Peripheral blood samples were obtained to isolate white blood cells and extract genomic DNA. High-throughput whole exome sequencing for candidate pathogenic genes in the proband was completed by the Huada Gene Technology Co. Ltd (Shenzhen, China). Sequencing showed a novel heterozygous missense mutation (a G to A transition at nucleotide 2582) in exon 22 of the *SLC12A3* gene, which resulted in a substitution of histidine for arginine at position 816 of the LRP1B protein and caused the occurrence of disease.

#### CONCLUSION

This is the first report of a new pathogenic mutation in *SLC12A3*. Further functional studies are particularly necessary to explore potential molecular mechanisms.

**Key words:** Gitelman syndrome; *SLC12A3*; High-throughput sequencing; Bioinformatics analysis; Case report

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**Core tip:** To screen for possible pathogenic loci in a patient with Gitelman syndrome by high-throughput exome sequencing and to explore the relationship between the genotype and phenotype. Sequencing showed a novel heterozygous missense mutation (a G to A transition at nucleotide 2582) in exon 22 of *SLC12A3* gene, which resulted in a

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substitution of histidine for arginine at position 816 of the LRP1B protein and caused the occurrence of disease.

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## INTRODUCTION

Gitelman syndrome (GS) is an inherited autosomal recessive renal tubular disorder that was first described by Gitelman in 1966. The main clinical manifestations include hypokalemia, hypomagnesemia, hypocalciuria, and hypochloremic metabolic alkalosis<sup>[1-3]</sup>. GS is often found in infants and young children with growth retardation and convulsions. Patients usually have normal blood pressure. The prevalence of GS ranges from 1/1000 to 9/10000. It is easily neglected due to their mild clinical manifestations and good prognosis. Several studies have shown that GS may be associated with chondrocalcinosis and dysglycemia; in severe cases, the patients may also develop ventricular arrhythmia and progressive renal insufficiency, which can be highly dangerous.

The main pathogenic gene in GS is *SLC12A3*, which encodes for thiazide-sensitive NaCl cotransporter. The rapid development of gene sequencing technology in recent years has facilitated the gene diagnosis<sup>[4-6]</sup>. According to expert consensus, the sequencing gene panels for GS should include the *SLC12A3*, *CLCNKB*, and *HNF1B* genes<sup>[7]</sup>. Whole exome sequencing (WES) can detect exon regions of over 20000 genes at a time. With the decrease in its price, WES has been increasingly used in clinical diagnosis<sup>[8]</sup>. Therefore, we applied WES for the genetic analysis in a clinically confirmed GS patient. In addition to *SLC12A3*, the most common gene associated with GS, we also detected *CLCNKB* and *HNF1B*<sup>[9-11]</sup>. We report a patient with clinically confirmed GS and determined the relevant gene mutation loci in an attempt to further improve our understanding of this disease.

## CASE PRESENTATION

### Chief complaints

A sudden onset of limb weakness without obvious cause, followed by limb numbness/stiffness, which was accompanied by palpitation.

### History of present illness

The patient was a 16-year-old male. He was admitted in January 2018 due to limb weakness and stiffness for two years. Two years ago, the patient had a sudden onset of limb weakness without obvious cause, followed by limb numbness/stiffness, which was accompanied by palpitation. Examination in a local hospital revealed hypokalemia, which was improved after potassium supplementation. However, the above symptoms recurred 2 mo ago due to cold, and the patient was admitted to our hospital for further treatment.

### History of past illness

He denied any other medical conditions.

### Personal and family history

There was no history of consanguineous marriage in the pedigree of three generations. The study was approved by the Ethics Committee of Shanxi Provincial People's Hospital, Taiyuan, China. The proband and his family members signed the informed consent.

### Physical examination upon admission

The thyroid gland was not large. There was no obvious abnormality in the heart and lungs.

### Laboratory examinations

Blood analysis: potassium, 2.64 mmol/L; sodium, 133.10 mmol/L; chlorine, 96.20 mmol/L; magnesium, 0.510 mmol/L; triglycerides, 1.64 mmol/L; blood pH, 7.35; standard bicarbonate, 25.60 mmol/L; and total carbon dioxide, 20.00 mmol/L. Urine analysis showed: calcium, 0.12 mmol/24 h; magnesium 2.200 mmol/24 h, phosphorus, 2.19 mmol/24 h; during the same period the blood potassium was 3.05 mmol/L and magnesium was 0.562 mmol/L. Circadian and pulsatile secretion of adrenocorticotrophic hormone and cortisol were normal. Baseline renin-angiotensin-aldosterone system test: Angiotensin I (37 °C), 49.94 µg/L; angiotensin I (4 °C), 6.87 µg/L; aldosterone, 149.05 ng/L; renin activity, 31.87 UG/L per hour, and aldosterone/renin activity 0.47. The average 24-h ambulatory blood pressure was 105/71 mmHg.

### Imaging examinations

No abnormality was seen on X-ray chest film, abdominal ultrasound, thyroid ultrasound, bilateral kidney and renal vascular ultrasound, adrenal ultrasound, and adrenal thin-slice computed tomography. Electrocardiogram showed sinus tachycardia at 105 beats/min.

### WES and bioinformatics analysis

**DNA extraction:** Peripheral venous blood (2 mL) was collected with heparin as anticoagulant. Genomic DNA was isolated from peripheral blood lymphocytes using OMEGA SE Blood DNA Kit and then sent to the Shenzhen Huada Gene Technology Co. Ltd for WES.

**Bioinformatics analysis:** Quality control of the raw reads was managed *via* FastQC<sup>[12]</sup>. Sequences were aligned to human reference genome hg19 using the Burrows-Wheeler Aligner<sup>[13]</sup>. The duplicate reads were removed by the Samblaster<sup>[14]</sup>. The INDEL was re-aligned using GATK realignment and base quality score recalibration was performed. We used five kinds of software to analyze variation, including GATK, Samtools, Freebayes, Platypus, and Varscan2, to ensure the accuracy of identification. Marginal variants were annotated in databases including dbSNP, 1000 Genomes Project, dbNSFP, and ClinVar<sup>[15-17]</sup>. The possible pathogenic mutations on *SLC12A3*, *CLCNKB*, and *HNF1B* genes were analyzed, and the relevant literature was searched according to these loci.

### Gene detection

The quality control results of the raw reads (Fastq) are shown in Figures 1 and 2. The average value of base qualities was larger than 30 (accuracy: 99.9%).

WES identified a total of 214137288 reads, among which 99.83% could be mapped to the human reference genome, and the duplicate reads accounted for 11.81%. The mean depth was 282X, which exceeded the general exome sequencing depth (Table 1).

A total of 67537 mutations were identified by bioinformatics analysis, including 55184 SNPs and 12353 INDELs (Figure 3). After dbSNP annotation, 94% of the SNPs were annotated in dbSNP, while only 35% of the INDELs could be annotated in dbSNP.

Mutations in *SLC12A3*, *CLCNKB*, and *HNF1B3* genes were filtered based on the following conditions: (1) The variant is located on an exon; (2) The variation does not belong to synonymous mutation; and (3) Population frequency is greater than 0.001.

After filtering, only one missense heterozygous mutation in the *SLC12A3* gene was left. Its population frequency was unknown. Most mutation prediction software such as Polyphen2 HDIV, SIFT, and FATHMM predicted it as a harmful mutation. The mutation information is shown in Table 2, and the mutation of exon 22 reported by another paper is shown in Table 3.

## FINAL DIAGNOSIS

According to the typical symptoms, laboratory tests, and gene analysis, the patient was diagnosed with GS.

## TREATMENT

The patient was given potassium therapy with antisterone.

## OUTCOME AND FOLLOW-UP

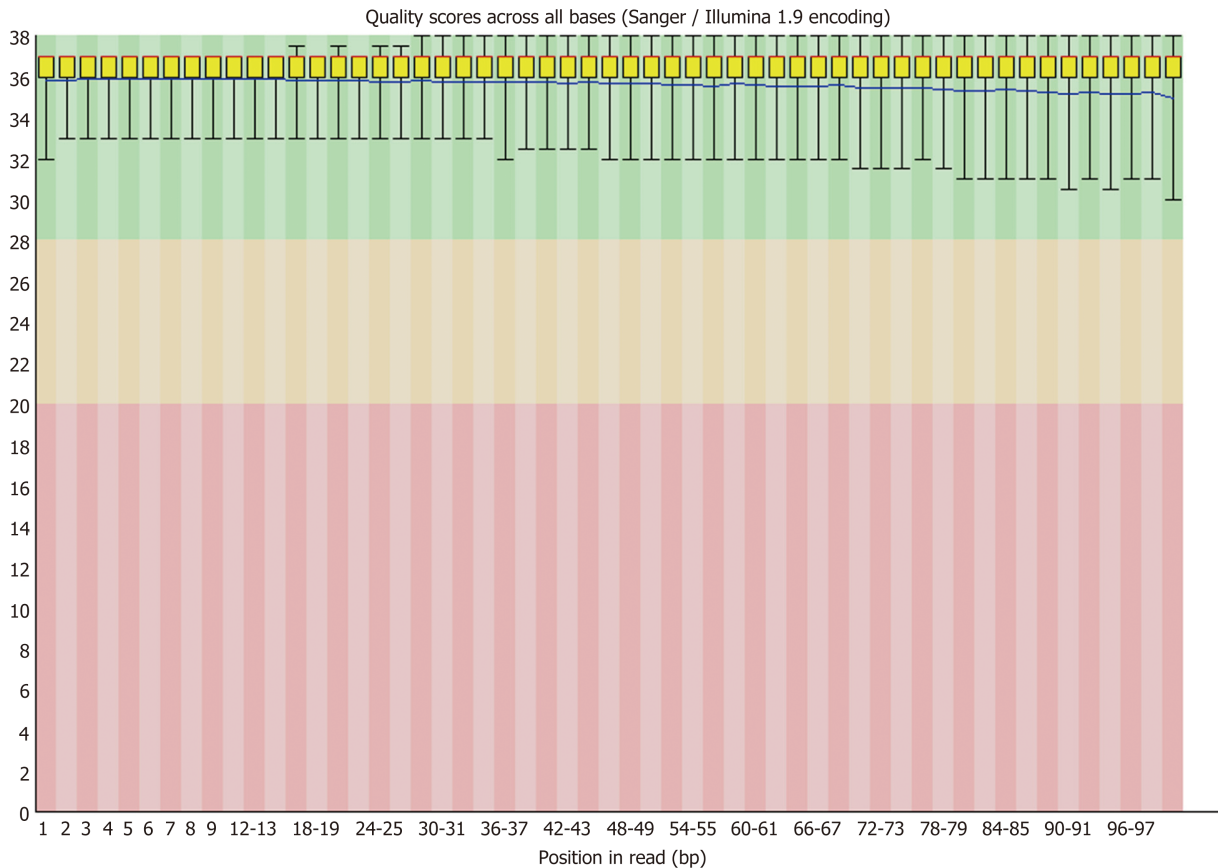


Figure 1 Raw reads of exome sequencing.

The patient recovered well and was discharged 7 d later. Regular detection of potassium is necessary.

## DISCUSSION

WES can detect the exon information of all genes at one time. With the decreased cost of high-throughput next-generation sequencing, WES has been increasingly applied in clinical diagnoses. In the present study, we used WES to further clarify the gene mutations in our patient. After bioinformatics analysis and population frequency filtering, we found a non-synonymous mutation in *SLC12A3* gene. A G2582A heterozygous mutation has also been reported in this site in the literature<sup>[18]</sup>.

Mutation analysis of the *SLC12A3* gene in our patient and his family members revealed a heterozygous missense mutation of G-to-A transition at nucleotide position 2582 within exon 22. An autosomal recessive disease does not present its traits in the heterozygous state. It occurs only when a pair of alleles is homozygous or compound heterozygotes of a recessive pathogenic gene. However, Balavoine *et al*<sup>[19]</sup> detected two mutation sites in the *SLC12A3* gene in most GS patients and only one mutation site in a small number of GS patients. In addition, patients with two mutation sites have more severe clinical symptoms than those with only one mutation site. GS is an autosomal recessive hereditary disease, and it does not occur in carriers. Current clinical studies have not found a significant correlation between GS genotype and phenotype.

With the decreased cost of sequencing and better understanding of diseases, the concept of precision medicine has been widely recognized over the past two years. Precision medicine represents the future direction of medical development. The core of precision medicine is to precisely identify pathogenic gene sites or pathogenic loci by gene sequencing and carry out targeted therapy according to pathogenic genes or pathogenic sites.

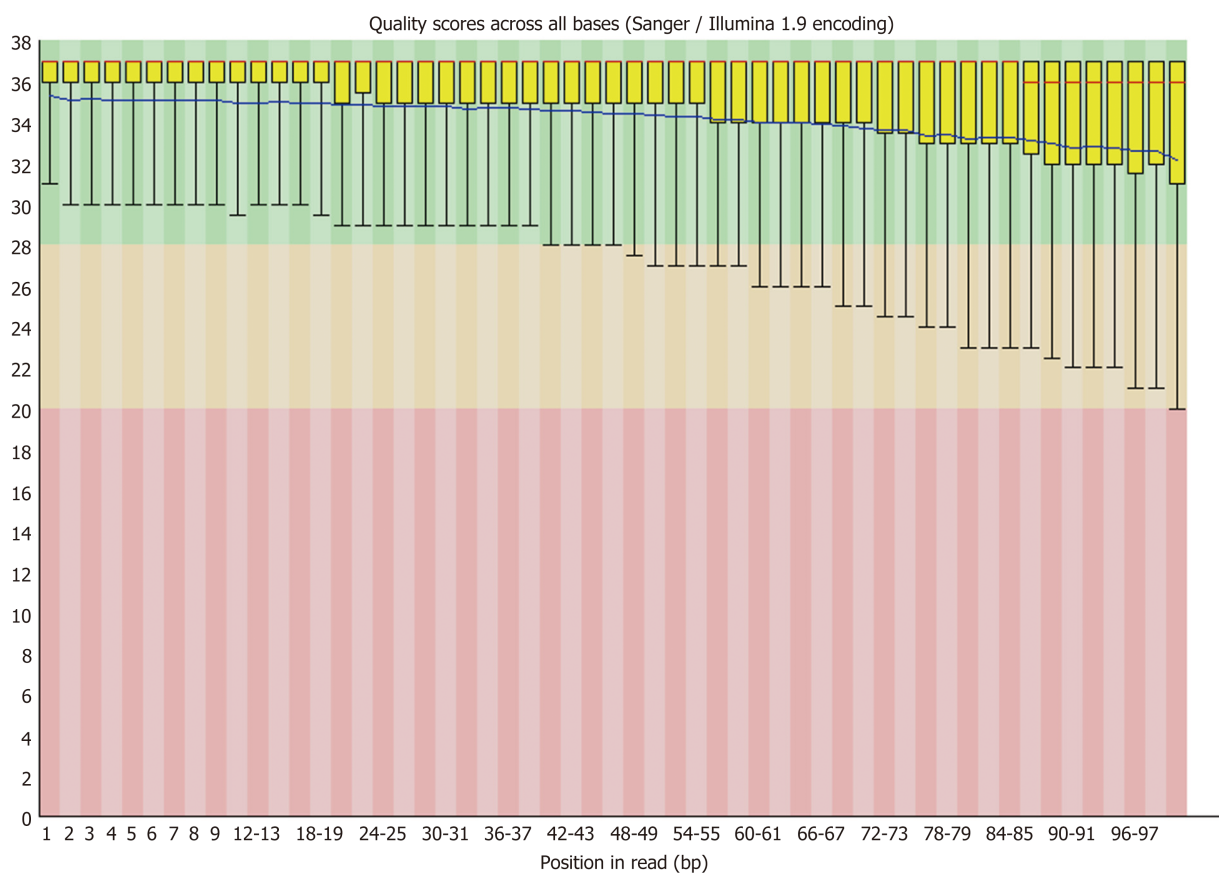


Figure 2 Quality control results of exome sequencing.

## CONCLUSION

A novel heterozygous missense mutation (a G to A transition at nucleotide 2582) in exon 22 of the *SLC12A3* gene is the first report of a new pathogenic mutation in *SLC12A3*. Further functional studies are particularly necessary to explore potential molecular mechanisms.

**Table 1** Reads alignment and sequencing depth

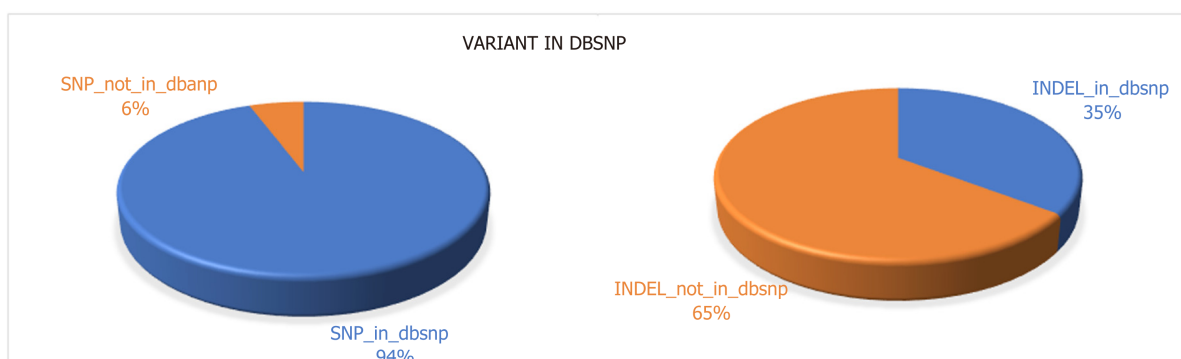
Total reads	Mapped reads	Duplicate reads	Mean depth
214137288	99.83%	11.81%	282X

**Table 2** Candidate genes

Type	Information
Gene	<i>SLC12A3</i>
RNA	NM_000339
Exon	exon22
DNA mutation	G2582A
AA mutation	R861H
Mutation frequency	50%
Population frequency	Unknown
Polyphen2_HDIV	D, D, D
FATHMM	D
MutationTaster	D
MutationAssessor	L
LRT	D
SIFT	T

**Table 3** Mutation in exon 22 of *SLC12A3* gene

Exon	Mutation	Pmid
exon22	Glv876Ser	17654016
exon22	Leu849His	17873326, 20229814
exon22	Arg852His	17873326, 20229814
exon22	Arg861Cys	27872838
exon22	Arg871His	21051746
exon22	Leu859Pro	21753071
exon22	Arg861Cys	21753071
exon22	Arg861His	Present study

**Figure 3** Number of variants.

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