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A Novel Heterozygous Mutation of Slc12a3 Gene in a Chinese Pedigree With Gitelman Syndrome

Peng LI*

Department of Pediatrics, Beijing Chaoyang Hospital, Capital Medical University, China

***Corresponding author:**

Peng Li,
Department of Pediatrics, Beijing Chaoyang Hospital, Capital Medical University. No. 8 Gongti South Road, Beijing, 100020, People's Republic of China,
E-mail: birdlee010@aliyun.com

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1. Abstract

1.1. Objective: Gitelman syndrome (GS) is an autosomal recessive tubular disorder characterized by metabolic alkalosis, hypokalemia, hypomagnesemia and hypocalciuria. GS is mostly caused by inactivating mutations of the SLC12A3 gene. The purpose of this study was to describe the clinical features of a GS patient and investigate the underlying mutations of SLC12A3 gene in the pedigree.

1.2. Methods: A patient suffering from muscle weakness was clinically diagnosed as GS. Clinical data of the proband were studied retrospectively. All of his family members were screened for SLC12A3 gene mutations. 26 exons and exon-intron boundaries of SLC12A3 gene were amplified by Polymerase Chain Reaction(PCR). PCR products were sequenced directly.

1.3. Results: The proband had hyperreninemia but hypoaldosteronemia, which was distinct from the cases previously reported. The proband and his sick brother were found to have the same compound heterozygous mutations (c.917C>T and IVS 14-8T>C) of SLC12A3 gene. Each mutation was detected in paternal and maternal genomic DNA, respectively. The proband's healthy brother had one mutation (c.917C>T) only. IVS 14-8T>C was a novel splicing site mutation that had never been reported.

1.4. Conclusion: Hypoaldosteronemia was found in a GS patient. A novel heterozygous splicing site mutation of the SLC12A3 gene was reported, expanding the spectrum of SLC12A3 gene mutations.

2. Introduction

Gitelman syndrome(GS) was an autosomal recessive renal tubular disorder mainly characterized by metabolic alkalosis, hypokalemia, hypomagnesemia and hypocalciuria[1-2]. The main responsible gene for GS was SLC12A3, encoding the thiazide sensitive sodium chloride cotransporter (NCCT) in the epithelial cells of distal convoluted tubule(DCT)[3-5]. The incidence of GS is around 1:25000[3]. Up to date, at least 492 mutations of SLC12A3 gene had been reported. Most mutations are missense/nonsense, splicing, deletions or insertions. Hypomagnesemia and hypocalciuria were generally regarded as the main clinical characteristics of GS. However, some cases of Bartter syndrome(BS) type III presented the same clinical features of GS[6]. Sometimes it was difficult to ascertain GS or BS type III without mutation analysis. The purpose of this study was to describe the clinical features of a GS patient and investigate the underlying mutations of SLC12A3 gene in his family.

3. Methods

3.1. Patient Selection

A 17-year-old male patient was admitted to hospital due to recurrent muscle weakness lasting for 3 years. He had no history of vomiting or diarrhea, no history of taking diuretics. Previous laboratory examinations showed hypokalemia. Oral supplementation of electrolytes was helpful. The proband's 14-year-old younger brother had the same symptoms while his parents and elder brother were healthy. All members of the pedigree agreed to join the

research.

3.2. Clinical Study

The proband underwent detailed physical examinations and laboratory examinations after admission. Renal biopsy was also performed. But his younger brother refused admission to hospital for economic problem.

3.3. Mutation Analysis

The clinical diagnosis of Gitelman syndrome was based on the findings of hypomagnesemia and hypocalciuria. Blood samples of all family members were obtained. Genomic DNA was extracted from peripheral blood cells using. 27 pairs of primers were used to amplify the 26 exons and exon-intron boundaries of SLC12A3 gene (2 pairs of primers for exon 1) by Polymerase Chain Reaction (PCR). PCR products were sequenced directly.

All family members or their guardians agreed the mutations analysis of SLC12A3 gene. And they also agreed to publish the outcome of the research. The mutation analysis was approved by the Ethics Committee of Beijing Chaoyang Hospital. The research abided by the principles of Helsinki Declaration.

4. Results

4.1. Clinical Findings of the Proband

The proband's blood pressure was 110/70mmHg. His body weight was 55 kg and his height was 170cm. Laboratory examination results were showed in (Table 1). He had hypokalemia, metabolic alkalosis, hypomagnesemia and hypocalciuria. The renin-angiotensin-aldosterone system was activated. The plasma renin activity and angiotensin II level were elevated both supinely and uprightly. However, the plasma aldosterone level was not elevated so much.

Table 1: Main laboratory findings of the proband

Variable		Test value	Normal range
Serum			
Na+ (mmol/L)		146.3	130-150
K+ (mmol/L)		3.04	3.5-5.5
Cl- (mmol/L)		96.6	96-108
Ca2+ (mmol/L)		2.83	2.25-2.75
Mg2+ (mmol/L)		0.48	0.7-1.3
HCO3-(mmol/L)		27.3	22-27
PH		7.464	7.35-7.45
Renin-angiotensin-aldosterone system			
Supine	Plasma renin activity (ng/ml.min)	0.6	0.1-0.5
	Angiotensin II (ng/L)	199.8	55.3-115.3
	Plasma aldosterone (pmol/L)	8.8	27.4-443.8
Upright	Plasma renin activity (ng/ml.min)	0.7	0.1-0.5
	Angiotensin II (ng/L)	208.4	55.3-115.3
	Plasma aldosterone (pmol/L)	25.1	27.4-443.8
24h urine			
Na+ (mmol/L)		194.3	130-260
K+ (mmol/L)		100.2	25-100
Cl- (mmol/L)		263.2	170-250
Ca2+ (mmol/L)		0.21	2.5-7.5

4.2. Genetic Findings

Two mutations of the SLC12A3 gene (c.917C>T and IVS 14-8T>C) were detected in the family (Figure 1). Each mutation was heterozygous. Neither mutation was found in 50 healthy controls. c.917C>T was a missense mutation in codon 304 that changed amino acid threonine to methionine (p.Thr304Met). IVS 14-8T>C was speculated to be a splicing site mutation. The pedigree chart was displayed in (Figure 2). The proband and his sick brother both carried the two mutations. Each mutation was inherited from paternal and maternal DNA, respectively. His healthy brother had one mutation (c.917C>T) only.

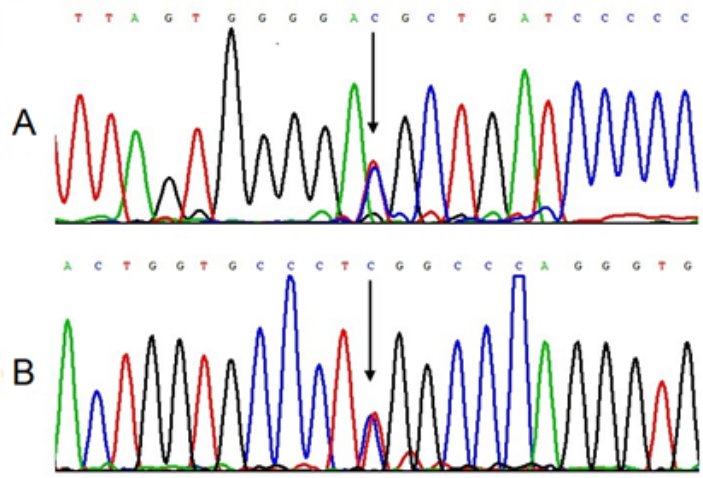

Figure 1: Genetic analysis of the SLC12A3 gene.
Legend: A, c.917C>T in exon 7; B, IVS 14-8T>C in exon 14. Arrows indicate the mutation position.

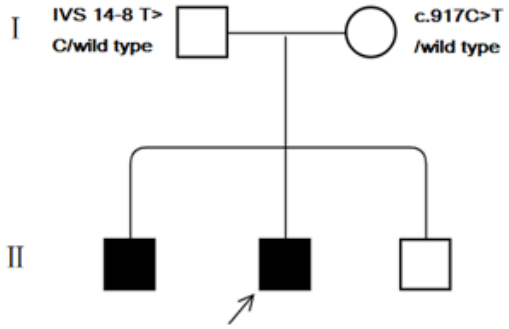

Figure 2: Pedigree chart of the family with GS.

5. Discussion

Gietlman syndrome used be considered as a subtype of Bartter syndrome since they were both salt-losing tubular disorders presenting hypokalemic metabolic alkalosis. The majority of GS patients carried SLC12A3 gene mutations while BS had its own responsible genes such as CLCNKB, ROMK, KCNJ1, BSND, CLCNKA, or MAGED2 [7]. The proband in this study had hypomagnesemia and hypocalciuria. So we make the diagnosis of GS and performed the mutation analysis of the SLC12A3 gene thereafter. Interestingly, although the proband had elevated serum renin activity and angiotensin II level, his plasma aldosterone level was not as high as expected. We speculated that it might be the result of the compensation of the body for previous salt supplementation might suppress the activation of renin-angiotensin-aldosterone system to some extent. The mutation c.917C>T (p.Thr304Met) had been described elsewhere [8]. It was a loss-of-function mutation that was found in a patient presenting both GS and primary hyperaldosteronism. IVS 14-8T>C was a novel splicing site mutation which had never been reported before. The healthy brother and healthy father carried this mutation only while the proband and his sick brother carried both mutations. It was speculated that IVS 14-8T>C might affect the splicing of SLC12A3 exons. Although nearly 500 mutations of SLC12A3 gene had been reported, there were no widely accepted hot-spot mutations. Some essays noted that Thr60Met was a hot-spot mutation in Chinese GS patients[9-10], but it was not found in the pedigree of our study. To make sure the hot-spot mutations of GS, more patients should take the mutation analysis of SLC12A3 gene.

6. Conclusion

In conclusion, we reported a pedigree of Gitelman syndrome from China and a novel splicing site mutation of SLC12A3 gene was revealed, expanding the spectrum of SLC12A3 gene mutations. This might be helpful for better understanding of the disease.

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