

# Consideration of the diagnosis of hypertension accompanied with hypokalaemia: monism or dualism?

Journal of International Medical Research

2018, Vol. 46(7) 2944–2953

© The Author(s) 2018

Reprints and permissions:

[sagepub.co.uk/journalsPermissions.nav](http://sagepub.co.uk/journalsPermissions.nav)

DOI: 10.1177/0300060518768154

[journals.sagepub.com/home/imr](http://journals.sagepub.com/home/imr)



Qingguo Lü<sup>1</sup>, Yajie Dong<sup>1</sup>, Heng Wan<sup>2</sup>,  
Yuwei Zhang<sup>1</sup>, Lizhi Tang<sup>1</sup>, Fang Zhang<sup>1</sup>,  
Zhe Yan<sup>1</sup> and Nanwei Tong<sup>1</sup>

## Abstract

This case report describes a 53-year-old male patient with persistent hypertension and hypokalaemia. Laboratory tests showed that the patient had hypokalaemia, hypocalcaemia and reduced urine calcium/creatinine. Levels of aldosterone and renin activity were increased significantly. Serum levels of adrenocorticotrophic hormone, plasma total cortisol level, 24-h urinary-free cortisol, catecholamines, thyroid stimulating hormone and free tetraiodothyronine were normal. A novel single heterozygous mutation (c.836T>G [E6]) was found after full sequencing of the solute carrier family 12 member 3 (*SLC12A3*) gene exons. The patient was diagnosed as having primary hypertension with Gitelman syndrome (GS). These findings triggered the careful consideration of whether a monistic or dualist approach to the diagnosis of this patient was the most appropriate. Monism may not always be the most appropriate approach for the diagnosis of coexistent hypertension and hypokalaemia. Consideration should be given to the possibility of the independent existence of distinct diseases (i.e. dualism) when secondary hypertension cannot be confirmed by conventional examinations and when a genetic diagnosis is crucial. As a common cause of hypokalaemia with a high level of clinical phenotypic variation, GS does not conform to the usual diagnostic criteria. It should also be noted that single heterozygous *SLC12A3* gene mutations can cause disease symptoms and other genetic mutations might be involved in the pathogenesis of GS.

<sup>1</sup>Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China

<sup>2</sup>Department of Internal Medicine, Xi'an Road Community Health Service Centre, Chengdu, Sichuan Province, China

## Corresponding author:

Nanwei Tong, Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, 37 Guoxue Lane, Wuhou District, Chengdu, Sichuan 610041, China.

Email: [buddyjun@hotmail.com](mailto:buddyjun@hotmail.com)



## Keywords

Diagnosis, hypertension, hypokalaemia, Gitelman syndrome, gene analysis

Date received: 22 June 2017; accepted: 7 March 2018

## Introduction

Hypertension is very common in adults and it is usually classified as ‘primary’ or ‘secondary’ hypertension. Primary hypertension is the most common form.<sup>1</sup> Secondary hypertension is usually considered if hypertension and hypokalaemia are present simultaneously and can be found in conditions such as primary aldosteronism, Cushing’s syndrome, pheochromocytoma, and some types of congenital adrenal cortical hyperplasia.<sup>1</sup>

Gitelman syndrome (GS) is an autosomal recessive disorder characterized by hypokalaemia, hypomagnesaemia, hypochloraemic alkalosis and hypocalciuria. It is caused by mutations of the solute carrier family 12 member 3 (*SLC12A3*) gene, which encodes the thiazide-sensitive sodium/chloride co-transporter (NCCT).<sup>2</sup> The prevalence of GS is estimated to be 25 cases per one million population.<sup>3</sup> The patient with GS may be asymptomatic or present with muscle weakness or paralysis.<sup>3</sup> Hypokalaemia is the most obvious feature of GS.<sup>3</sup> Hypertension is not a common feature of GS; in contrast, patients with GS often have hypotension.<sup>3</sup> Whether the diagnosis of GS can be excluded if hypertension and hypokalaemia are present simultaneously, and whether secondary hypertension can be confirmed, is not known.

This case report describes a patient with hypertension and hypokalaemia who was eventually diagnosed as having primary hypertension with GS through clinical and laboratory tests to exclude secondary hypertension, and novel mutations that

were found in the *SLC12A3* gene by gene analyses, which triggered the careful consideration of how patients like this are diagnosed in clinical practice.

## Case report

A 53-year-old male patient was admitted to the Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu, China in July 2015 with the chief complaints of elevated blood pressure (BP) for about 13 years and detection of low levels of potassium in the serum for 2 years. About 13 years ago, the patient had experienced dizziness without obvious predisposing causes. He visited a local hospital and was found to have elevated BP (158/100 mmHg). Since then, his BP has always been higher than 140/90 mmHg according to his own monitoring. After self-medication using the Chinese traditional medicine Zhenju Jiangya in tablet form (the specific dose of which was not known), the BP fluctuated around 120–130/70–80 mmHg. Eight years ago, the patient replaced Zhenju Jiangya with 5 mg amlodipine besylate orally once daily, which lowered the BP to about 120/80 mmHg. A low level of serum potassium (2.93 mmol/l) was found during a health check-up 2 years ago. Occasionally, he felt tremors without numbness, weakness or other discomfort, but further diagnosis and treatment were not given. Thereafter, hypokalaemia was found several times during laboratory examinations, but the patient did not pay attention to these

findings. Three months ago, he agreed to have a routine examination at a local hospital. Analyses of blood biochemistry revealed potassium to be 2.95 mmol/l, calcium to be 2.19 mmol/l, and magnesium to be 0.85 mmol/l. Enhanced magnetic resonance imaging of the abdomen did not show any abnormality of the bilateral adrenal glands. Then, the patient came to West China Hospital, Sichuan University for further diagnosis and treatment. Physical examination revealed a body temperature of 36.4°C, heart rate of 82 beats/min, respiratory rate of 17 times/min, BP of 146/94 mmHg, height of 168 cm, weight of 67 kg, body mass index of 23.74 kg/m<sup>2</sup> and waist circumference of 88 cm. His consciousness was clear with negative pathological signs. Muscle strength in the upper and lower limbs was grade 5. The examinations undertaken in this case were approved by the Ethics Committee of West China Hospital, Sichuan University and the patient provided written informed consent before undergoing the examinations detailed in this report.

Laboratory parameters for this patient were determined by the Department of Laboratory Medicine, West China Hospital. Levels of potassium, calcium, and magnesium in serum and urine were determined using an automatic biochemical analyser (Cobas® 8000 modular analyser; Cobas, Basel, Switzerland). Arterial blood gas was analysed using a blood gas analyser (GEM 3000; Beckman Coulter, Brea, CA, USA). Urine analysis was completed using fully automated urine chemistry analysers (UF-1000i and UC-3500; Sysmex Corporation, Kobe, Japan). Renin activity and aldosterone levels in plasma were measured by radioimmunoassay. Serum adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), free tetraiodothyronine (FT<sub>4</sub>), plasma total cortisol (PTC) and 24-h urinary-free cortisol (UFC) were determined by electrochemical luminescence. High performance liquid chromatography

was employed to measure levels of adrenaline and noradrenaline in plasma.

The main laboratory test results of the patient are shown in Table 1. These results

**Table 1.** Laboratory results for a 53-year-old male patient with persistent high blood pressure and hypokalaemia who was admitted to hospital for further diagnostic tests and treatment.

| Test items                              | Test value | Reference values |
|---|------------|------------------|
| <b>Blood biochemicals</b>               |            |                  |
| K, mmol/l                               | 3.21       | 3.5–5.3          |
| Na, mmol/l                              | 143.4      | 137.0–147.0      |
| Cl, mmol/l                              | 102.2      | 99.0–110.0       |
| Ca, mmol/l                              | 1.97       | 2.1–2.7          |
| Mg, mmol/l                              | 0.92       | 0.67–1.04        |
| PO <sub>4</sub> , mmol/l                | 0.99       | 0.81–1.45        |
| <b>Analysis of arterial blood gases</b> |            |                  |
| pH                                      | 7.361      | 7.35–7.45        |
| PO <sub>2</sub> , mmHg                  | 78.9       | 90–110           |
| PCO <sub>2</sub> , mmHg                 | 42.0       | 35–45            |
| HCO <sub>3</sub> , mmol/l               | 23.3       | 22–27            |
| <b>Urinalysis</b>                       |            |                  |
| Specific gravity                        | 1.015      | 1.010–1.025      |
| pH                                      | 7.00       | 4.60–8.00        |
| <b>24-hour urine analysis</b>           |            |                  |
| K, mmol/24 h                            | 105.13     | 40–80            |
| Ca, mmol/24 h                           | 0.70       | 2.5–7.5          |
| Cr, mmol/24 h                           | 10.28      | 7–18             |
| Ca/Cr, mmol/ mmol                       | 0.068      | >0.1             |
| Mg, mmol/24 h                           | 6.48       | 3.0–5.0          |
| P, mmol/24 h                            | 13.55      | 22–48            |
| <b>Hormone tests</b>                    |            |                  |
| PRA, ng/ml.h                            | >7.8       | 0.05–0.80        |
| Angiotensin II, ng/l                    | 54.17      | 28.2–52.2        |
| Aldosterone, ng/dl                      | 34.93      | 4.5–17.5         |
| ARR, ng/dl:ng/ml.h                      | 2.45       | <20              |
| ACTH, ng/l                              | 31.27      | 5.0–78.0         |
| PTC (8:00am), nmol/l                    | 336.20     | 147.3–609.3      |
| 24-hUFC, µg/24h                         | 107.1      | 20.26–127.55     |
| Noradrenaline, ng/l                     | 283        | 272–559          |
| Adrenaline, ng/l                        | 119        | 54–122           |
| TSH, mU/l                               | 1.43       | 0.27–4.20        |
| FT <sub>4</sub> , pmol/l                | 17.94      | 12–22            |

PRA, plasma renin activity; Cr, creatinine; Ca/Cr, calcium/creatinine; ARR, aldosterone-to-renin ratio; ACTH, adrenocorticotropic hormone; PTC, plasma total cortisol; UFC, urinary-free cortisol; TSH, thyroid stimulating hormone; FT<sub>4</sub>, free tetraiodothyronine.

showed mild hypocalcaemia and hypokalaemia with normal levels of magnesium in serum, but total calcium and calcium/creatinine in urine were reduced significantly compared with the reference range. Analysis of arterial blood gas revealed pH and  $\text{HCO}_3$  levels to be at the lower limit of normal. Plasma levels of aldosterone and renin activity were increased significantly, while ACTH, PTC, 24-h UFC, adrenaline, noradrenaline, TSH and  $\text{FT}_4$  levels were normal.

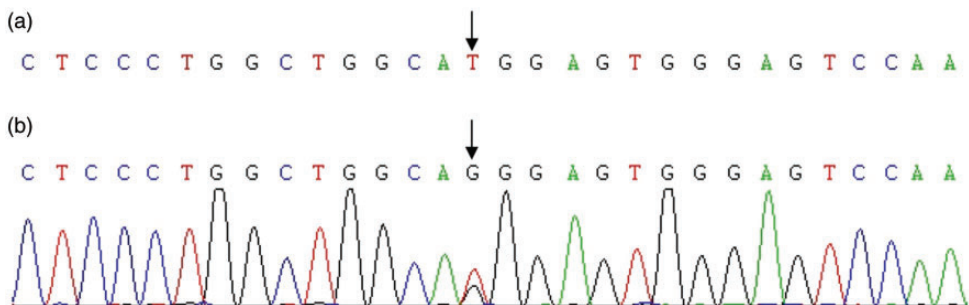
To further confirm the diagnosis, a full exon scan was conducted. Amplification and sequence analysis of the *SLC12A3* gene were completed in the Endocrinology and Metabolic Diseases Research Room of West China Hospital and Joy Orient Translational Medicine Research Centre, Beijing, China. Blood samples from the patient were taken, then next-generation sequencing and DNA sequencing were performed. Table 2 shows the primer and

product length of the mutation sites of the *SLC12A3* gene. Gene mutation (nucleotide c.836T> G [E6], amino-acid mutation p. M279R) was found after full sequencing of *SLC12A3* exons, suggesting that encoded mutated proteins would be harmful. This single heterozygous mutation (carrier) was novel and has not been reported previously. The sequencing peak map of the patient is shown in Figure 1.

The patient was diagnosed as having GS based on genetic testing, medical history and laboratory tests. No evidence of secondary hypertension (e.g. Cushing's syndrome, primary aldosteronism) was found and no mutations associated with primary hypertension were detected by full sequencing of exons. The patient's BP could be controlled by consumption of only one antihypertensive drug at a conventional dose. Hence, we concluded that the diagnosis was primary hypertension. Therefore,

**Table 2.** Primer and product length of the *SLC12A3* gene mutation site.

| Primer name | Primer sequence                     | Melting temperature | Product length  |
|-------------|-------------------------------------|---------------------|-----------------|
| SLC12A3-IF  | ACGTAGGTCGCATG<br>GTGAATGAGTAGGCAAA | 60 °C               | 1240 base pairs |



**Figure 1.** The sequencing peak map of a 53-year-old male patient with persistent high blood pressure and hypokalaemia who was admitted to hospital for further diagnostic tests and treatment. Chromatogram of *SLC12A3* exon region: (a) NCBI reference sequence; (b) patient's sequence. The colour version of this figure is available at: <http://imr.sagepub.com>.

the final diagnosis of this patient was stage-1 primary hypertension (low-risk) and GS. These two disorders were treated separately. For primary hypertension, the antihypertensive agent was replaced with 4 mg perindopril tablets orally once daily. BP was maintained at about 110–125/70–80 mmHg during 6-month follow-up. For GS, 500 mg potassium chloride sustained-release tablets orally three times daily and 20 mg spironolactone tablets orally twice daily were prescribed. Serum levels of potassium fluctuated around 3.5–4.0 mmol/l and the activity of renin and level of aldosterone decreased within 6-month follow-up. Magnesium supplements were not administered because serum levels of magnesium were within the normal range.

## Discussion

Hypertension and hypokalaemia are relatively common disorders.<sup>4</sup> For patients with hypokalaemia, it is more important to search for the underlying cause of the hypokalaemia than to supplement with potassium. The main causes of hypokalaemia are inadequate intake of potassium, excessive discharge of potassium (including through the digestive tract, kidney or skin), transport of potassium from the extracellular environment to the intracellular milieu, impact of certain foods (e.g. liquorice preparations) and barium poisoning. Dietary readjustment sometimes corrects hypokalaemia. Evidence of secondary causes of hypertension should also be investigated: drug-resistant hypertension (BP is higher than 140/90 mmHg upon treatment with three or more types of antihypertensive drugs), hypertension with hypokalaemia, hypertension with an adrenal incidentoma, and family history of early-onset hypertension.

In this current report, the case of a middle-aged male patient with hypertension and hypokalaemia was described. In theory,

this patient could have been considered a typical case of secondary hypertension, so evidence of this was investigated after hospital admission. A range of tests for hormone levels and function were carried out, but there was no evidence for primary aldosteronism, Cushing's syndrome or other features of secondary hypertension. At this point, should we have continued looking for relevant evidence of secondary hypertension or should we have changed our minds? The following questions were considered: (i) was the hypertension associated with hypokalaemia in this case; and (ii) could we explain this case by the same pathogenesis (monism)? During subsequent diagnostic procedures, hypertension and hypokalaemia were temporarily considered as two independent aspects to explore the aetiology. First, full exon sequencing was undertaken, and it found a mutation in the *SLC12A3* gene (c.836T> G [E6]; p.M279R), which confirmed the diagnosis of GS and provided a reasonable explanation for the hypokalaemia. However, there was no relevant secondary factors or genetic abnormalities associated with hypertension, thereby suggesting a diagnosis of primary hypertension.

While investigating this current case, it was difficult to explain the hypertension accompanied by hypokalaemia by one pathogenesis or disease, so we had to adjust our thinking and analyse the causes separately. The possibility of the independent presence of primary hypertension and hypokalaemia in a single patient required careful consideration. For example, we have previously diagnosed a patient as having primary hypertension with hypokalaemic periodic paralysis through genetic analysis (*SCN4A* gene mutation) (unpublished data). During clinical diagnosis, physicians often try to explain two or more clinical manifestations as being caused by one disease or pathophysiological mechanism, which is called 'monism'. Based

on the above diagnostic process for this current case, a monistic approach can sometimes restrict clinical thinking. In some cases, 'dualism' or 'pluralism' may be more appropriate for diagnosis, as these approaches allow physicians to expand their thinking and avoid a missed diagnosis or misdiagnosis. Meanwhile, this case also demonstrated that undertaking full exon sequencing to identify genetic mutations can play a key role in searching for the cause of hypokalaemia, especially in patients whose clinical manifestations are not specific. GS has been reported to be a common cause of hypokalaemia due to renal potassium loss.<sup>5</sup>

The pathogenesis of GS involves the mutation of the *SLC12A3* gene, which encodes the renal thiazide-sensitive NCCT.<sup>2</sup> *SLC12A3* is located on chromosome 16q13 and is 55 000 nucleotides long with 26 exons.<sup>6</sup> Human NCCT is expressed mainly in the distal convoluted tubules, where 5–10% of the sodium ions and chloride ions from glomerular filtration are reabsorbed.<sup>7,8</sup> Mutations of the *SLC12A3* gene can lead to the abnormal structure and/or dysfunction of the NCCT, which leads to dysfunction in the reabsorption of sodium ions and chloride ions.<sup>8</sup> This phenomenon results in hypovolaemia and activation of the renin–angiotensin–aldosterone system (RAAS), which causes hypokalaemia and metabolic alkalosis.<sup>3</sup> The chloride ion clearance test, along with clinical manifestations and laboratory tests, is very important in the diagnosis of GS.<sup>9</sup> Furosemide can cause a significant increase in the clearance of chloride ions in GS patients, but hydrochlorothiazide does not affect clearance in this way.<sup>9</sup> However, in many cases, the clinical manifestations of GS and laboratory tests are not typical, and the chloride ion clearance test is very complicated.<sup>9</sup> Therefore, detection of mutations in the *SLC12A3* gene are crucial for the diagnosis of GS.

Gitelman syndrome used to be considered a rare disease. Some researchers have reported an incidence of approximately 1 per 50 000 individuals with the prevalence of heterozygous carriers being about 1 per 100 individuals<sup>8,10</sup> and of heterozygous carriers in Gypsy populations being about 1 per 50 individuals.<sup>11</sup> There is no nationwide data on the prevalence of GS. With the development of gene technology, increasing numbers of patients with hypokalaemia have been diagnosed with GS and its prevalence is far greater than previously thought. For example, according to the mutation screening of 1852 Japanese patients, one heterozygous mutation carrier was found in every 15.6 individuals, and the incidence of GS in Japanese subjects was 10.3 per 10 000.<sup>12</sup> Generally, the symptoms of GS are mild, and as it is not a threat to life, the SNP has not been removed by the pressure of natural selection. The patient can survive long enough to pass on the mutation to their offspring, which explains its relatively high prevalence. GS is the most commonly inherited renal tubular disease.<sup>5</sup>

The clinical phenotype of GS shows considerable heterogeneity.<sup>6</sup> There is no significant association between genotype and phenotype.<sup>13,14</sup> Heterogeneity in the GS phenotype has been documented in individuals with different mutations and in individuals with the same mutation.<sup>15</sup> However, the symptoms of homozygous mutants are, in general, more serious than those of heterozygous mutants, and their risk of other complications such as diabetes mellitus and chronic kidney damage are increased.<sup>16</sup> Information about long-term outcomes in GS is lacking. It was reported that GS may be associated with glomerular proteinuria due to abnormalities of the glomerular basement membrane.<sup>17,18</sup> Chronic kidney disease might develop in GS patients due to either chronic hypokalaemia, which is associated with tubulointerstitial nephritis, tubule vacuolization, and cystic changes, or



volume depletion and increased renin–angiotensin–aldosterone, which may contribute to renal damage and fibrosis.<sup>16,19,20</sup> Patients may not have any symptoms, and GS has been diagnosed as hypokalaemia detected in a conventional physical examination.<sup>3</sup> Some patients exhibit hypokalaemia-related weakness, flaccid paralysis, halophilia and polyuria.<sup>3</sup> In addition to hypokalaemia-related symptoms, BP must also be considered in the diagnosis of GS. One study in a Japanese population reported that heterozygous mutation carriers of GS do not show BP changes.<sup>12</sup> However, patients with a homozygous mutation or compound heterozygous mutations show lower BP, and around 2% of hypotension is caused by GS.<sup>13</sup> Dysfunction in reabsorption of sodium ions and chloride ions in the distal convoluted tubules of GS patients may result in hypovolaemia and can induce hypotension.<sup>3</sup> However, individuals with compound heterozygous mutations and homozygous mutations could compensate for defects in NCCT function by increasing salt intake, and RAAS activation may also have a compensatory role.<sup>7</sup> Patients may not necessarily present with hypotension.<sup>21</sup> Hence, hypertension should not exclude a diagnosis of GS.<sup>20</sup> The patient in this report had both hypertension and hypokalaemia. We did not exclude the diagnosis of GS simply because of the coexistent hypertension. After the exclusion of secondary hypertension, he was subsequently diagnosed with GS based on the full exon sequencing genetic analysis. This process highlights the importance of gene technology in the diagnosis of these patients.

As specific pathogenetic gene SNPs for GS, *SLC12A3* mutations in different domains either abolish or weaken the function of NCCT with different molecular mechanisms.<sup>7,22</sup> At least five potential mechanisms have been reported to explain how *SLC12A3* mutations cause GS: impairing protein synthesis, impairing protein

processing, impairing insertion of an otherwise functional protein into the plasma membrane, impairing the functional properties of the cotransporter and accelerating protein removal or degradation.<sup>7,22</sup> To date, only a small proportion of the mutations have been identified by functional experiments. As a newly found mutation located in the second transmembrane domain, the function of M279R has not been identified.<sup>23</sup> Mutations in the same domain may play a similar role in NCCT impairment and we speculate that the functional mechanism of the M279R mutation might mimic other mutations in the same domain.<sup>22,23</sup> Further animal and molecular biology experiments are needed to verify this speculation. In this current case, no other cause of hypokalaemia was identified except the definite M279R mutation. Therefore, in our opinion, this novel mutation in the *SLC12A3* gene can explain the current clinical manifestations and a diagnosis of GS can be obtained. Serum magnesium was normal in this patient with mild hypokalaemia, which may have been due to mild condition of this patient (only one allele mutation and short course of hypokalaemia). However, the patient's urine magnesium rose, so hypomagnesaemia may occur in the future if the condition continues to progress. A previous study reported normal serum magnesium in male patients from two GS families,<sup>24</sup> suggesting that hypomagnesaemia may not be an essential feature of GS as there is high heterogeneity.

Since the first mutation of the *SLC12A3* gene was identified as the cause of GS in 1996,<sup>6</sup> more than 500 mutation sites have been found, including missense mutations, shear mutations, nonsense mutations, and reading frame shifting mutations.<sup>25</sup> Missense mutations are the most common, but 'hotspot' mutations have not been identified.<sup>22</sup> Compound heterozygous mutations are more common than homozygous mutations.<sup>25</sup> Most patients have compound

heterozygous mutations with two different mutations in two alleles.<sup>25</sup> In this report, a novel mutation of the *SLC12A3* gene (c.836T> G [E6]) was identified, but there was only one mutation on two alleles, which is a single heterozygous mutation. According to the laws of autosomal recessive inheritance, a single heterozygous mutation should not lead to disease development, so why did this patient present with severe hypokalaemia? In the light of previous reports, only one mutation in the *SLC12A3* gene is present in about 40% of GS patients.<sup>5</sup> GS is an autosomal recessive inherited disease, so another undetected mutated allele point may be involved in GS pathogenesis. There are four possible reasons why we could not identify another mutation site in our patient. First, the mutation site may have been located on the regulatory sequences of *SLC12A3* that did not undergo sequencing analysis (e.g. 5' or 3' untranslated regions or deep regions of introns). Secondly, single-exon analysis involving one or more exons in gene rearrangements is difficult. Thirdly, expression and function of NCCT can be affected by acquired modifications. Fourthly, the combined effect of other mutations cannot be excluded. A previous report found that the R438H mutation of the chloride voltage-gated channel K<sub>b</sub> (*CLCNKB*) gene may have a role to play in GS pathogenesis in addition to *SLC12A3*.<sup>26</sup> A study of 132 GS patients in Belgium without *SLC12A3* mutations or only one allele mutation showed that the parvalbumin gene could be a candidate gene in GS.<sup>27</sup> Therefore, other mutated genes may be involved in the pathogenesis of GS.

In conclusion, this current case report describes a male patient with hypertension and hypokalaemia who was diagnosed with GS and primary hypertension by genetic analysis. This diagnostic process has highlighted the fact that monism might not always be the best approach for the

diagnosis of co-existent hypertension and hypokalaemia. Consideration should be given to the independent existence of high blood pressure and hypokalaemia when patients cannot be diagnosed with secondary hypertension using conventional examinations. Genetic analyses then become crucial and have resulted in growing numbers of patients with hypokalaemia being diagnosed with GS. There is considerable heterogeneity of this disease between genotype and phenotype. It should also be noted that single heterozygous *SLC12A3* gene mutations can cause disease symptoms and other genetic mutations might be involved in the pathogenesis of GS.

### Acknowledgements

We express thanks to the Joy Orient Translational Medicine Research Centre, Beijing, China for the work of gene amplification and sequence analysis.

### Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

### Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

### References

1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. Epub ahead of print 13 November 2017. DOI: 10.1161/HYP.000000000000065.
2. Melander O, Orho-Melander M, Bengtsson K, et al. Genetic variants of thiazide-sensitive NaCl-cotransporter in Gitelman's



- syndrome and primary hypertension. *Hypertension* 2000; 36: 389–394.
3. Parmar MS and Bhimji SS. Gitelman Syndrome, <https://www.ncbi.nlm.nih.gov/books/NBK459304/> (2017, accessed 2 February 2018).
  4. Kovesdy CP, Appel LJ, Grams ME, et al. Potassium homeostasis in health and disease: A scientific workshop cosponsored by the National Kidney Foundation and the American Society of Hypertension. *J Am Soc Hypertens* 2017; 11:783–800.
  5. Konrad M and Weber S. Recent advances in molecular genetics of hereditary magnesium-losing disorders. *J Am Soc Nephrol* 2003; 14: 249–260
  6. Mastroianni N, Bettinelli A, Bianchetti M, et al. Novel molecular variants of the Na-Cl cotransporter gene are responsible for Gitelman syndrome. *Am J Hum Genet* 1996; 59: 1019–1026.
  7. Riveira-Munoz E, Chang Q, Bindels RJ, et al. Gitelman's syndrome: towards genotype-phenotype correlations? *Pediatr Nephrol* 2007; 22: 326–332.
  8. Mastroianni N, De Fusco M, Zollo M, et al. Molecular cloning, expression pattern, and chromosomal localization of the human Na-Cl thiazide-sensitive cotransporter (SLC12A3). *Genomics* 1996; 35: 486–493.
  9. Peng XY, Jiang LP, Yuan T, et al. Value of chloride clearance test in differential diagnosis of Gitelman Syndrome. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2016; 38: 275–282.
  10. Riveira-Munoz E, Chang Q, Godefroid N, et al. Transcriptional and functional analyses of SLC12A3 mutations: new clues for the pathogenesis of Gitelman syndrome. *J Am Soc Nephrol* 2007; 18: 1271–1283.
  11. Bouwer ST, Coto E, Santos F, et al. The Gitelman syndrome mutation, IVS9+1G>T, is common across Europe. *Kidney Int* 2007; 72: 898.
  12. Tago N, Kokubo Y, Inamoto N, et al. A high prevalence of Gitelman's syndrome mutations in Japanese. *Hypertens Res* 2004; 27: 327–331.
  13. Lee JW, Lee J, Heo NJ, et al. Mutations in SLC12A3 and CLCNKB and their correlation with clinical phenotype in patients with Gitelman and Gitelman-like Syndrome. *J Korean Med Sci* 2016; 31: 47–54.
  14. Lü Q, Zhang Y, Song C, et al. A novel SLC12A3 gene homozygous mutation of Gitelman syndrome in an Asian pedigree and literature review. *J Endocrinol Investig* 2015; 39: 333–340.
  15. Coto E, Rodriguez J, Jeck N, et al. A new mutation (intron 9 +1 G>T) in the SLC12A3 gene is linked to Gitelman syndrome in Gypsies. *Kidney Int* 2004; 65: 25–29.
  16. Tseng MH, Yang SS, Hsu YJ, et al. Genotype, phenotype, and follow-up in Taiwanese patients with salt-losing tubulopathy associated with SLC12A3 mutation. *J Clin Endocrinol Metab* 2012; 97: E1478–E1482.
  17. Berry MR, Robinson C and Karet Frankl FE. Unexpected clinical sequelae of Gitelman syndrome: hypertension in adulthood is common and females have higher potassium requirements. *Nephrol Dial Transplant* 2013; 28: 1533–1542.
  18. Demoulin N, Aydin S, Cosyns JP, et al. Gitelman syndrome and glomerular proteinuria: a link between loss of sodium-chloride cotransporter and podocyte dysfunction? *Nephrol Dial Transplant* 2014; 29(suppl 4): iv117–iv120.
  19. Balavoine AS, Bataille P, Vanhille P, et al. Phenotype-genotype correlation and follow-up in adult patients with hypokalaemia of renal origin suggesting Gitelman syndrome. *Eur J Endocrinol* 2011; 165: 665–673.
  20. Walsh SB, Unwin E, Vargas-Poussou R, et al. Does hypokalaemia cause nephropathy? An observational study of renal function in patients with Bartter or Gitelman syndrome. *QJM* 2011; 104: 939–944.
  21. Hsu YJ, Yang SS, Chu NF, et al. Heterozygous mutations of the sodium chloride cotransporter in Chinese children: prevalence and association with blood pressure. *Nephrol Dial Transplant* 2009; 24: 1170–1175.
  22. Li C, Zhou X, Han W, et al. Identification of two novel mutations in SLC12A3 gene in two Chinese pedigrees with Gitelman Syndrome and review of literature. *Clin Endocrinol (Oxf)* 2015; 83: 985–993.
  23. Syrén ML, Tedeschi S, Cesareo L, et al. Identification of fifteen novel mutations in

- the SLC12A3 gene encoding the Na-Cl cotransporter in Italian patients with Gitelman syndrome. *Hum Mutat* 2002; 20: 78.
24. Lin SH, Cheng NL, Hsu YJ, et al. Intrafamilial phenotype variability in patients with Gitelman syndrome having the same mutations in their thiazide-sensitive sodium/chloride cotransporter. *Am J Kidney Dis* 2004; 43: 304–312.
  25. Luo J, Yang X, Liang J, et al. A pedigree analysis of two homozygous mutant Gitelman syndrome cases. *Endocr J* 2015; 62: 29–36.
  26. Zelikovic I, Szargel R, Hawash A, et al. A novel mutation in the chloride channel gene, CLCNKB, as a cause of Gitelman and Bartter syndromes. *Kidney Int* 2003; 63: 24–32.
  27. Riveira-Munoz E, Devuyst O, Belge H, et al. Evaluating PVALB as a candidate gene for SLC12A3-negative cases of Gitelman's syndrome. *Nephrol Dial Transplant* 2008; 23: 3120–3125.