Genetic Analysis of SLC12A3 Gene in Chinese Patients with Gitelman Syndrome

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Background: The incidence of Gitelman syndrome (GS) has been increasing in our hospital. The aim of this study was to explore the diagnostic accuracy and features of SLC12A3 gene in Chinese patients with GS.

Material/Methods: We searched the literature about Chinese patients with GS in the PubMed database up to July 2018 and also included 8 GS Chinese patients from our hospital in our analysis that explored the features of SLC12A3 gene. We divided all the patients into 3 groups according to diagnostic consensus. Complete compliance was defined to mean containing 2 allelic mutations, partial compliance to mean one allelic mutation, and clinical compliance to mean no mutations.

Results: Totally, 137 patients were enrolled in this study and 90 mutations were counted. Missense mutations accounted for over 72% in Chinese GS patients and the most common one was Thr60Met. According to the consensus, there were 102 patients (74.5%) in the complete compliance group, 31 patients (22.6%) in the partial compliance group, and only 4 patients (2.9%) in the clinical compliance group.

Conclusions: The SLC12A3 gene analysis in Chinese GS patients revealed that the most common mutation was Thr60Met, one of the missense mutations. Most of the patients were in the complete compliance group (i.e., 2 allelic mutations); the other cases might be explained by gene rearrangement.

MeSH Keywords: DNA Mutational Analysis • Gitelman Syndrome • Solute Carrier Family 12, Member 3

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Background

Gitelman syndrome (GS) is an inherited tubular disease characterized by hypokalemia and metabolic alkalosis, accompanied by hypocalcemia, urinary calcium, and hypomagnesaemia. The dysfunction of thiazide-sensitive Na-Cl co-transporter (NCCT) in the distal convoluted tubules, caused by SLC12A3 gene mutation, lead to GS. According to the consensus and guidance on Gitelman syndrome published in 2016 [1] and the 2017 Expert Consensus for the Diagnosis and Treatment of Patients with GS [2], the detection of biallelic inactivating mutations in SLC12A3 gene is established as the diagnostic criteria of GS [1,2]. However, it has been reported that approximately 18–40% of patients clinically diagnosed as GS carry only 1 allelic mutation by SLC12A3 gene as detected by direct sequencing [3]. And among the mutations detected at SLC12A3, gene rearrangements may account for 26% [3]. Therefore, this study aimed to analyze the mutations of SLC12A3 gene in Chinese patients with GS, and explore its diagnostic coincidence rate.

Material and Methods

We searched the literature published by Chinese researchers on the PubMed database up to July 2018 using 2 keywords, namely, a combination of “Gitelman Syndrome” and “China”. In the retrieved literature, we included those describing the information for mutations in SLC12A3 gene of GS patients (such as the number of mutant alleles, type and location of mutation, predictive effect, etc.) into our study. And we also included 8 unrelated Chinese GS patients based on clinical and genetic diagnosis in our hospital from September 2015 to April 2018 in the study analysis. According to the diagnostic criteria based on consensus, we divided all the patients into 3 groups. Complete compliance was defined to mean having 2 allelic mutations, partial compliance to mean 1 allelic mutation, and clinical compliance to mean no mutations.

Results

Analysis of diagnostic coincidence rate

As shown in Table 1 [4–24], in total, 21 initial publications identifying SLC12A3 gene mutations in GS were retrieved. We divided the number of mutated allele into 3 groups, biallelic, monoallelic, and none inactivating mutation only, corresponding to the complete compliance group, partial compliance group, and clinical compliance group respectively. Of 137 cases, biallelic inactivating mutations were identified in 102 patients which accounted for 74.5% of the cases. And among the biallelic inactivating mutations, 28 cases were homozygous (27.5%) and 74 cases were compound heterozygous (72.5%). Monoallelic inactivating mutation was identified in 31 patients (22.6%). None inactivating mutation only appeared in 4 patients (2.9%). According to the consensus criteria, the complete compliance rate was 74.5%, the partial compliance rate was 22.6%, and the clinical coincidence rate was 2.9%.

Characterization of the SLC12A3 gene mutations

In our study, 90 different mutations were counted, and were spread throughout the gene. There are 21 novel variants reported by Chinese researchers for the first time (Table 1), and 14 of these were missense mutations. As shown in Figure 1, over 72% of SLC12A3 gene mutations were missense mutations, whereas nonsense, synonymy, deletion, insertion, and splice-site mutations were less frequently observed. Small deletions or insertions mutations account for approximately 17%, splice 6%, synonymy 2%, and nonsense 3%.

Figure 2 showed the distribution and frequency of the 248 mutated alleles in the 26 exons of the SLC12A3 gene. Four recurrent mutations including Thr60Met, Asp486Asn, Arg913Gln and Arg928Cys, and we found an allele frequency >3%. These recurrent mutations were mainly caused by the missense changes of amino acid in 81 alleles (67 patients). And the most common mutation in our study was Thr60Met found in 42 alleles (33 patients). Asp486Asn was found in 21 alleles (18 patients), Arg913Gln in 10 alleles (9 patients), and Arg928Cys in 8 alleles (7 patients).

Discussion

Because of similar clinical manifestations, GS is considered a subtype of Bartter Syndrome having hypomagnesaemia and hypocalciuria. A few years ago, the molecular basis of GS was revealed by Simon et al. They first demonstrated a linkage of GS to the locals encoding the renal NCC, an integral membrane protein consisting of 1030 amino acids with 12 transmembrane and intercellular N and C-terminal domains [8,25]. Thereafter, a series of studies identified the human SLC12A3 gene, which encodes the NCC. This gene is about 55 kb in length and locate on the long arm of chromosome 16q consisting of 26 separate exons.

By searching the human genome database (HGMD 2017.1), we found that 488 mutations of the SLC12A3 gene have been discovered in patients with GS [8]. And these mutations include missense mutations, shear mutations, deletion mutations, nonsense mutations, reading frame shift mutations, and other mutations [8]. Most mutations are compound heterozygous mutations, and missense mutation was the most common one. In our study, compound heterozygous mutations were discovered in
Table 1. SLC12A3 mutations identified in 137 Chinese patients with Gitelman syndrome.

| Homo/Het/CoHet | No. | Position | Predicted effect | Reference |
|----------------|-----|----------|------------------|-----------|
| **Biallelic inactivating mutations in SLC12A3 (n=102)** |
| CoHomo | 1 | Exon24 | Arg928Cys | 4 |
| | | Exon2 | Ala122Ala |
| | | Exon11 | Thr465Thr |
| | 2 | Exon16 | Arg655Leu | 5 |
| | | Exon1 | Thr60 Met |
| | 3 | Exon1 | Thr60Met | 6 |
| | | Exon15 | Arg655His |
| CoHet | 4 | Exon1 | Thr60Met | 7 |
| | 5 | Exon15 | Asn640Ser* | 8 |
| | | Exon21 | Asp841Gly* |
| | 6 | Exon10 | Cys430Gly | 9 |
| | | Exon2 | c.346−353delACTGATGG* |
| | 7 | Exon1 | Thr60Met | 10 |
| | | Exon2 | c.346−353delACTGATGG |
| | 8 | Exon1 | Thr60Met | 10 |
| | | Exon10 | Cys430Gly |
| | 9 | Exon10 | Gly439Val | 10 |
| | | Exon24 | c.2883−2884delAG |
| | 10 | Exon14 | Leu571Pro | 10 |
| | | Exon26 | c.2969insGCT |
| | 11 | Exon8 | Asn359Lys | 10 |
| | | Exon10 | Gly439Val |
| | 12 | Exon8 | Del n7426−n7438 and Ins(accgaaaatntt) | 10 |
| | | Exon23 | Arg913Gln |
| | 13 | Exon17 | Ser710X | 10 |
| | | Exon24 | Arg919Cys |
| | 14 | Exon12 | Asp486Asn | 10 |
| | | Exon20 | Gly800Trp |
| | 15 | Exon1 | Thr60 Met | 11 |
| | | Exon2 | Ala122Ala |
| | | Exon8 | c.965−1_976del13ins12 |
| | 16 | Exon8 | Asn359Lys | 11 |
| | | Exon9 | Thr382Met |
Table 1 continued. SLC12A3 mutations identified in 137 Chinese patients with Gitelman syndrome.

| No. | Position | Predicted effect | Reference |
|-----|----------|-----------------|-----------|
| CoHet | Exon23 | Arg913Gln | 17 |
| Exon8 | Asn359Lys | 12 |
| Exon12 | Asp486Asn | 18 |
| Exon12 | Asp486Asn | 12 |
| Exon24 | Arg928Cys | 19 |
| Exon23 | Arg913Gln | 18 |
| Exon14 | c.1670-8C>T | 20 |
| Exon23 | Arg913Gln | 5 |
| Exon14 | c.1670-8C>T | 18 |
| Exon14 | c.1670-8C>T | 21 |
| Exon1 | Thr60 Met | 16 |
| Exon7 | Thr304Met | 22 |
| Exon10 | Cys430Gly | 23 |
| Exon21 | 1028frameshift | 24 |
| Exon24 | c.850-851delAG | 25 |
| Exon24 | c.850-851delAG | 26 |
| Exon5 | Leu215Pro | 14 |
| Exon8 | Asn359Lys | 27 |
| Exon10 | Arg399Cys | 14 |
| Exon7 | Thr304Met | 28 |
| Exon12 | Asp486Asn | 14 |
| Exon15 | Gln617Arg | 29 |
| Exon3 | Ala166Thr | 30 |
| Exon16 | Val677Met | 14 |
| Exon25 | Ser976Phe | 31 |
| Exon17 | Leu700Val | 14 |
| Exon23 | Arg913Gln | 32 |
| Exon10 | Thr428Ile | 14 |
| Exon12 | Asp486Asn | 33 |
| Exon3 | Trp151X | 14 |
| Exon9 | Ala370Pro | 14 |
**Table 1 continued.** SLC12A3 mutations identified in 137 Chinese patients with Gitelman syndrome.

| Homo/Het/CoHet | No. | Position | Predicted effect | Reference |
|---------------|-----|----------|------------------|-----------|
| CoHet         | 34  | Exon20   | Gly800Arg        |           |
|               |     | Exon2    | Glu131Lys        | 14        |
|               |     | Exon5    | Gly201Asp        |           |
|               | 35  | Exon2    | Leu215Pro        |           |
|               |     | Exon21   | Trp844X          |           |
|               | 36  | Exon1    | Tyr70Cys         | 14        |
|               |     | Exon22   | Arg861Cys        |           |
|               | 37  | Exon10   | Cys430Gly        | 14        |
|               |     | Exon24   | Arg928Cys        |           |
|               |     | Exon17   | Ser710X          |           |
|               | 38  | Exon3    | c.486-490delTACGGinsA | 14 |
|               |     | Exon10   | Cys430Gly        |           |
|               |     | Exon16   | Val659Met        |           |
|               | 39  | Exon4    | Gly196Val        | 14        |
|               |     | Exon24   | c.2877_2878del    |           |
|               |     | Exon1    | Thr60Met         | 15        |
|               | 40  | Exon1    | Arg642His*       |           |
|               |     | Exon8    | Thr339ile*       | 15        |
|               |     | Exon8    | Asn359Lys*       |           |
|               | 41  | Exon8    | Thr339ile*       | 15        |
|               |     | Exon15   | Arg642His*       |           |
|               |     | Exon23   | Arg904Gln        |           |
|               | 42  | Exon1    | Thr60Met         | 15        |
|               |     | Exon23   | Arg904Gln        |           |
|               | 43  | Ivvs7,ex8| IVS7-1 G > A g.7427_7438delinsCGAAAATTTT | 15 |
|               |     | Exon23   | Arg904Gln        |           |
|               | 44  | Ivvs7,ex8| IVS7-1 G > A g.7427_7438delinsCGAAAATTTT | 15 |
|               |     | Exon10   | Cys421Phe        |           |
|               | 45  | Exon1    | The60Met         | 16        |
|               |     | Exon1    | c.234delG*       |           |
|               | 46  | Exon15   | Arg642His*       | 16        |
|               |     | Exon3    | c.486-490delTACGGinsA | 16 |
|               | 47  | Exon10   | Gly439Ser        | 6         |
|               |     | Exon15   | Ser615Leu        |           |
|               | 48  | Exon21   | c.2454_2461delCAAGGCCC | 6 |
|               |     | Exon23   | Arg913Gln        |           |
|               | 49  | Exon1    | Thr60Met         | 6         |
|               |     | Exon13   | Asn534Lys        |           |

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**CLINICAL RESEARCH**

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Table 1 continued. SLC12A3 mutations identified in 137 Chinese patients with Gitelman syndrome.

| Homo/Het/CoHet | No. | Position | Predicted effect | Reference |
|----------------|-----|----------|------------------|-----------|
| CoHet          | 50  | Exon1    | Arg83Gln         | 6         |
|                |     | Exon24   | Arg928Cys        |           |
|                | 51  | Exon12   | Asp486Asn        | 6         |
|                |     | Exon6    | c.806 ins TTGGCGCTGTCATGGTCA |           |
|                | 52  | Exon12   | Asp486Asn        | 6         |
|                |     | Exon10   | Arg399Cys        |           |
|                | 53  | Intron3  | c.506-1G>A       | 6         |
|                |     | Exon3    | Leu170Gln        |           |
|                | 54  | Exon16   | Thr649Met        | 6         |
|                |     | Exon15   | His637Tyr        |           |
|                | 55  | Exon24   | Arg928Cys        | 6         |
|                |     | Exon15   | Arg642Cys        |           |
|                | 56  | Exon8    | Asn359Lys        | 6         |
|                |     | Exon15   | Gln617Arg        |           |
|                | 57  | Exon10   | Gly439Ser        | 6         |
|                |     | Exon15   | Arg642Cys        |           |
|                | 58  | Exon22   | Arg861His        | 6         |
|                |     | Exon14   | Asn566Lys        |           |
|                | 59  | Exon4    | Thr180Lys        | 6         |
|                |     | Exon1    | Thr60Met         |           |
|                | 60  | Exon6    | Leu272Pro        | 6         |
| Intron7/Exon8  | 61  | Exon4    | Gly190Val*       | 9         |
|                |     | Exon10   | Gly439Val*       | 9         |
|                | 62  | Exon1    | Thr60Met         | 9         |
|                |     | Exon10   | Cys430Gly*       |           |
|                | 63  | Exon1    | Thr60Met         | 9         |
|                |     | Exon11   | c.1384delG*      |           |
|                | 64  | Exon14   | Leu571Pro*       | 9         |
|                |     | Exon26   | c.2969insGCT*    |           |
|                | 65  | Exon1    | Thr60Met         | 9         |
|                |     | Exon12   | Asp486Asn        |           |
|                | 66  | Exon1    | Thr60Met         | 17        |
| Intron3        | 67  | Exon1    | Thr60Met         | 17        |
Table 1 continued. *SLC12A3* mutations identified in 137 Chinese patients with Gitelman syndrome.

| Homo/Het/CoHet | No. | Position | Predicted effect | Reference |
|---------------|-----|----------|------------------|-----------|
| CoHet         |     | Intron3  | c.506-1G>A       | 17        |
|               | 68  | Intron3  | c.506-1G>A       |           |
|               |     | Exon17   | Ser710X          |           |
|               | 69  | Exon8    | c.506-490delTACGGinsA | 17     |
|               |     | Exon8    | c.965-1_969delCGGACinsACCGAAA | |
|               | 70  | Exon1    | Thr60Met         | This study|
|               |     | Exon3    | Thr163Met        |           |
|               |     | Exon22   | Arg871His        |           |
|               | 71  | Exon1    | Arg83Gln         | This study|
|               |     | Exon3    | Thr163Met        |           |
|               |     | Exon22   | Arg871His        |           |
|               | 72  | Exon1    | Arg83Gln         | This study|
|               |     | Exon3    | Thr163Met        |           |
|               |     | Exon22   | Arg871His        |           |
|               | 73  | Exon1    | Thr60Met         | This study|
|               |     | Exon3    | Arg83Gln         |           |
|               |     | Exon22   | Arg871His        |           |
|               | 74  | Exon1    | Thr60Met         | This study|
|               |     | Exon3    | Thr163Met        |           |
|               |     | Exon22   | Arg871His        |           |
|               | 75  | Exon3    | Arg83Gln         | This study|
|               |     | Exon8    | Gly362Ser        |           |
|               | 76  | Exon17   | Ser710X          | 4         |
|               |     | Exon8    | c.976-977delGT   |           |
|               | 77  | Exon1    | Leu700Pro*       | 18        |
|               |     | Exon3    | Thr163Met        | 19        |
|               | 79  | Exon17   | Ser710X          | 4         |
|               |     | Exon1    | Thr60Met         | 10        |
|               | 81  | Exon23   | Arg913Gln        | 10        |
|               | 82  | Exon9    | Tyr386Cys        | 10        |
|               | 83  | Exon1    | Thr60Met         | 12        |
|               | 84  | Exon16   | Arg655Leu        | 5         |
|               | 85  | Exon1    | Thr60Met         | 5         |
|               | 86  | Exon1    | Thr60Met         | 5         |
Table 1 continued. SLC12A3 mutations identified in 137 Chinese patients with Gitelman syndrome.

| Homo/Het/CoHet | No. | Position | Predicted effect | Reference |
|----------------|-----|----------|------------------|-----------|
| Homo           | 87  | Exon1    | Thr60Met         | 5         |
|                | 88  | Exon12   | Asp486Asn        | 14        |
|                | 89  | Exon12   | Asp486Asn        | 14        |
|                | 90  | Exon12   | Asp486Asn        | 14        |
|                | 91  | Exon1    | Thr60Met         | 14        |
|                | 92  | Exon17   | Leu700Pro        | 14        |
|                | 93  | Exon12   | Asp486Asn        | 14        |
|                | 94  | Exon10   | Arg399Pro        | 20        |
|                | 95  | Exon16   | Arg655His        | 15        |
|                | 96  | Exon9    | Tyr386Cys*       | 15        |
|                | 97  | Exon1    | Thr60Met         | 6         |
|                | 98  | Exon1    | Thr60Met         | 9         |
|                | 99  | Exon1    | Thr60Met         | 9         |
|                | 100 | Exon1    | Thr60Met         | 9         |
|                | 101 | Exon23   | Arg896Gln        | 9         |
|                | 102 | Exon23   | Arg896Gln        | 21        |

Monoallelic inactivating mutations in SLC12A3 (n=31)

| Het            | No. | Position | Predicted effect | Reference |
|----------------|-----|----------|------------------|-----------|
|                | 103 | Exon24   | Arg919Cys        | 10        |
|                | 104 | Exon8    | Del n7426–n7438 and Ins(accgaaaatttt) | 10        |
|                | 105 | Exon14   | Phe545Leu        | 10        |
|                | 106 | Exon1    | Thr60Met         | 10        |
|                | 107 | Exon4    | Thr180Lys        | 22        |
|                | 108 | Exon22   | Leu849His        | 12        |
|                | 109 | Exon16   | Leu671Pro*       | 12        |
|                | 110 | Exon14   | Asn566Lys        | 5         |
|                | 111 | Exon6    | Gly264Ala        | 23        |
|                | 112 | Exon6    | M279R            | 24        |
|                | 113 | Exon12   | Asp486Asn        | 14        |
|                | 114 | Exon7    | Thr304Met        | 14        |
|                | 115 | Exon10   | Arg399Cys        | 14        |
|                | 116 | Exon15   | Ser615Leu        | 14        |
|                | 117 | Exon16   | Arg655Cys        | 14        |
|                | 118 | Exon1    | Thr60Met         | 15        |
|                | 119 | Exon12   | Asp486Asn        | 15        |
|                | 120 | Ivs16,ex17 | IVS16-2 A > G* | 15        |
Table 1 continued. SLC12A3 mutations identified in 137 Chinese patients with Gitelman syndrome.

| Homo/Het/CoHet | No. | Position | Predicted effect | Reference |
|----------------|-----|----------|------------------|-----------|
| Het            | 121 | Exon12   | Asp486Asn        | 6         |
|                | 122 | Exon14   | Asn566Lys        | 6         |
|                | 123 | Exon12   | Asp486Asn        | 6         |
|                | 124 | Exon16   | Arg655Leu        | 6         |
|                | 125 | Exon23   | Arg913Gln        | 6         |
|                | 126 | Exon23   | Arg913Gln        | 6         |
|                | 127 | Exon24   | Arg928Cys        | 6         |
|                | 128 | Exon12   | Asp486Asn        | 6         |
|                | 129 | Exon24   | Arg928Cys        | 6         |
|                | 130 | Exon12   | Asp486Asn        | 6         |
|                | 131 | Exon6    | c.806 ins TTGCGTGATCTCAGGCA | 6 |
|                | 132 | Exon1    | Thr60Met         | 9         |
|                | 133 | Exon3    | c.486-490delTACGGinsA | 17 |
| None inactivating mutations in SLC12A3 (n=4) |
|                | 134 |           |                  | 12        |
|                | 135 |           |                  | 12        |
|                | 136 |           |                  | 12        |
|                | 137 |           |                  | 12        |

Homo – homozygous; Het – heterozygous; CoHet – compound heterozygous; CoHomo – compound homozygous; * novel variant.

Although global hotspots have not yet been discovered, certain mutations occur frequently in specific populations. For example, on study found the top 3 in Japanese populations was R919C, L849H, and T180 K [19]. IVS9+1G >T was the most common one in Gypsy populations and another mutation c.1196_1202dup7bp was the most frequent in Italian patients [26]. Data from Shao et al. first showed that Thr60Met was the most common amino acid mutation in a Chinese population and possibly specific to Asian populations [9]. From then on, several studies supported this conclusion [12,17,26,27]. Consistent with previous studies, we also found that the most common mutation was Thr60Met. This suggested to us that screening for the Thr60Met mutation in a Chinese population can provide genetic consultation on GS. The results of 3 studies [26–28] found that Asp486Asn was a recurrent mutation. And in the study of Liu et al. [27], Arg913Gln was also found as a recurrent mutation. This suggested to us that Asp486Asn and Arg913Gln might also be the hotspots in Chinese GS patients. As for Arg928Cys, no study has indicated its mutation frequency. More studies are needed to prove whether it is a common mutation in the Chinese population.

Figure 1. Pattern of mutations by type at the SLC12A3 gene.
At present, we diagnose GS mainly on the basis of the 2 consensus areas. From the consensus, we can see that identification of biallelic inactivating mutations in the SLC12A3 gene is the criteria for establishing a diagnosis of GS. However, many patients were found to carry only one mutated allele by direct sequencing. According to a large cohort study about the SLC12A3 gene mutations in 448 patients with GS in France, 2 mutations were identified by direct genomic DNA sequencing in 315 patients (70%), while 1 mutation was identified in 81 patients (18%), and no mutation in 52 patients (12%) using direct sequencing [3]. The results of the study in a Chinese population by Ma et al. showed that 2 pathogenic SLC12A3 mutations were identified in 38 patients (70.4%), 1 mutation in 11 patients (20.4%) and no mutation in 5 patients (9.3%) using direct sequencing [26]. However, in the study of 67 Chinese GS patients by Liu et al., they discovered approximately 83.6% of their GS patients carried both allele mutations and 16.4% carried only one mutant allele [27]. In our study, we found 2 SLC12A3 gene mutations in 102 patients (74.5%), 1 SLC12A3 gene mutation in 31 patients (22.6%), and no SLC12A3 gene mutation in 4 patients (2.9%). This suggested to us that the compliance rate is influenced by the sample size and therefore more studies are needed to confirm our findings. Surprisingly, Vargas-Poussou et al. found that almost half of patients suspected of having only 1 mutation by direct sequencing had large genomic rearrangements on the other allele [3]. Therefore, we should use multiplex ligation-dependent probe amplification (MLPA) to screen those carrying only 1 mutated allele. At the same time, we should keep in mind that even after MLPA analysis, still some patients carry only 1 pathogenic mutation. In this case, mutations in the SLC12A3 intron or other genes may be potential second molecular defects. As we all know, patients with mutations in the CLCNKB gene, which is associated with Bartter syndrome, can present with a Gitelman-like phenotype. And according to the results of Vargas-Poussou et al., about a third of those having no mutation in the SLC12A3 gene have mutations in the CLCNKB gene [3]. Furthermore, recently Kong et al. reported a girl with mutations in both in the SLC12A3 gene and the CLCNKB gene, indicating a digenetic inheritance due to a genetic double-hit mechanism [29]. This might indicate that our failure to identify SLC12A3 gene mutations is probably due to misdiagnosis of the patients. Therefore, for those clinical compliance patients, with no mutations in the SLC12A3 gene, we should look for mutations in the CLCNKB gene. But whether we would detect the CLCNKB gene in complete compliance and partial compliance patients still needs more evidence.

Conclusions

This genetic analysis of the SLC12A3 gene in Chinese patients with GS showed us compound heterozygous mutations were more common than homozygous mutations, which accounted for 72.5%. Furthermore, we discovered that missense mutations accounted for over 72% of the different mutations found in the SLC12A3 gene. Four recurrent mutations were found in our study and the most common mutation was Thr60Met, which suggested to us that screening for the Thr60Met mutation in a Chinese population can provide genetic consultation for GS. Moreover, our study showed that the complete compliance rate was 74.5%, the partial compliance rate was 22.6%, and the clinical coincidence rate was 2.9% by direct sequencing according to consensus. Therefore, in order to increase the diagnostic rate, we suggest that we use MLPA to screen large genomic rearrangements in those carrying only a single mutated allele.

Ethical approval

This study does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest

None.
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