Genetic Analysis of *SLC12A3* Gene in Chinese Patients with Gitelman Syndrome

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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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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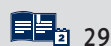https://www.medscimonit.com/abstract/index/idArt/916069
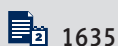
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Background

Gitelman syndrome (GS) is an inherited tubular disease characterized by hypokalemia and metabolic alkalosis, accompanied with 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 *SLCl2A3* gene as detected by direct sequencing [3]. And among the mutations detected at *SLC12A3*, gene rearrangements may account for ≥6% [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 hypomagnesemia 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
		Exon12	Asp486Asn	
	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(accgaaatttt)	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.

Homo/Het/CoHet	No.	Position	Predicted effect	Reference
CoHet		Exon23	Arg913Gln	
	17	Exon8	Asn359Lys	12
		Exon12	Asp486Asn	
	18	Exon12	Asp486Asn	12
		Exon24	Arg928Cys	
	19	Exon23	Arg913Gln	5
		Exon14	c.1670-8C>T	
	20	Exon23	Arg913Gln	5
		Exon14	c.1670-8C>T	
	21	Exon1	Thr60 Met	13
		Exon7	Thr304Met	
	22	–	T465P*	13
		Exon15	N611T*	
	23	Exon10	Cys430Gly	14
		Exon26	1028frameshift	
	24	Exon21	Trp844X	14
		Exon24	c.2850-2851delAG	
	25	Exon21	Trp844X	14
		Exon24	c.2850-2851delAG	
	26	Exon5	Leu215Pro	14
		Exon8	Asn359Lys	
	27	Exon10	Arg399Cys	14
		Exon7	Thr304Met	
	28	Exon12	Asp486Asn	14
		Exon15	Gln617Arg	
	29	Exon3	Ala166Thr	14
		–	Gly303Val	
	30	Exon16	Val677Met	14
		Exon25	Ser976Phe	
	31	Exon17	Leu700Val	14
		Exon23	Arg913Gln	
	32	Exon10	Thr428Ile	14
		Exon12	Asp486Asn	
	33	Exon3	Trp151X	14
		Exon9	Ala370Pro	

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

Homo/Het/CoHet	No.	Position	Predicted effect	Reference
CoHet		Exon20	Gly800Arg	
	34	Exon2	Glu131Lys	14
		Exon5	Gly201Asp	
	35	Exon5	Leu215Pro	14
		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	
	40	Exon1	Thr60Met	15
		Exon2	c.492_496delTACGGinsA*	
	41	Exon8	Thr339Ile*	15
		Exon8	Asn359Lys*	
	42	Exon1	Thr60Met	15
		Exon23	Arg904Gln	
	43	Ivs7,ex8	IVS7-1 G > A g.7427_7438delinsCCGAAAATTTT	15
		Exon23	Arg904Gln	
	44	Ivs7,ex8	IVS7-1 G > A g.7427_7438delinsCCGAAAATTTT	15
		Exon10	Cys421Phe	
	45	Exon1	The60Met	16
		Exon1	c.234delG*	
	46	Exon15	Arg642His*	16
		Exon3	c.486-490delTACGGinsA*	
	47	Exon10	Gly439Ser	6
		Exon15	Ser615Leu	
	48	Exon21	c. 2454_2461delCAAGGCCC	6
		Exon23	Arg913Gln	
	49	Exon1	Thr60Met	6
		Exon13	Asn534Lys	

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 TTGGCGTGGTCTCGGTCA	
	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	c.965-1_976delinsACCGAAAATTTT	
	61	Exon4	Gly196Val*	9
		Exon10	Gly439Val*	
	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	c.506-1G>A	
	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	
	68	Intron3	c.506-1G>A	17
		Exon17	Ser710X	
	69	Exon3	c.486-490delTACGGinsA	17
		Exon8	c.965-1_969delgCGGACinsACCGAAA	
		Exon8	c.976–977delGT	
	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	
	74	Exon1	Thr60Met	This study
		Exon3	Thr163Met	
		Exon22	Arg871His	
	75	Exon3	Arg83Gln	This study
		Exon8	Gly362Ser	
	76	Exon18	Gly729Val	This study
		Exon10	Gly439Ser	
	77	Exon1	Thr60Met	This study
		Exon3	Arg83Gln	
Homo	78	Exon17	Leu700Pro*	18
	79	Exon3	Thr163Met	19
	80	Exon17	Ser710X	4
	81	Exon1	Thr60Met	10
	82	Exon23	Arg913Gln	10
	83	Exon9	Tyr386Cys	10
	84	Exon1	Thr60Met	12
	85	Exon16	Arg655Leu	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	Exon3	c.486-490 TACGG→A	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	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 TTGGCGTGGTCTCGGTCA	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.
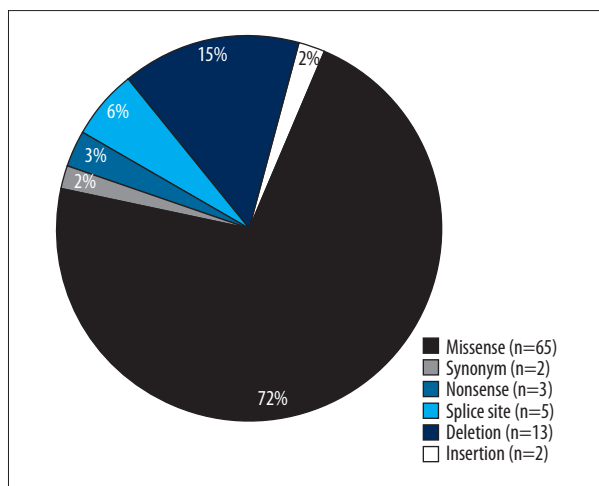
Figure 1. Pattern of mutations by type at the *SLC12A3* gene.

74 patients (54%) and missense mutation accounted for over 72% of the mutations found. Compound heterozygous mutations were detected in all the 8 patients diagnosed in our hospital and all of them were missense mutations. Among the mutations we analyzed, 21 were novel and 14 were missense.

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 mutations. 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.
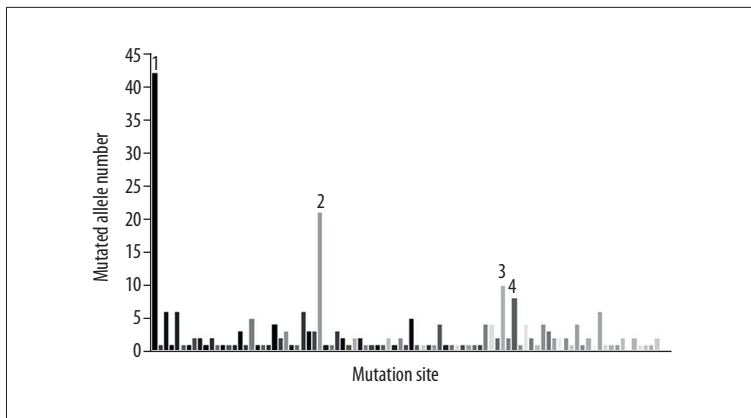
Figure 2. Frequency and distribution of the 90 counted mutations in 248 alleles. On the horizontal axis, each bar represents one mutation. Dotted line corresponds to an allele frequency >3%. #1 denotes p.Thr60Met: 42 alleles in 33 patients; #2 denotes p.Asp486Asn: 21 alleles in 18 patients; #3 denotes p.Arg913Gln: 10 alleles in 9 patients; and #4 denotes p.Arg928Cys: 8 alleles in 7 patients.

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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