Genetic and Clinical Analyses of 13 Chinese Families With Cystine Urolithiasis and Identification of 15 Novel Pathogenic Variants in SLC3A1 and SLC7A9

Chuangye Li†, Yongjia Yang‡, Yu Zheng‡, Fang Shen², Li Liu¹, Yanfang Li¹, Liping Li² and Yaowang Zhao¹*

1 Department of Urology, Hunan Children's Hospital, Changsha, China. 2 The Laboratory of Genetics and Metabolism, Hunan Children’s Research Institute (HCRi), Hunan Children’s Hospital, University of South China, Changsha, China

Background: Cystinuria is a rare genetic disorder characterized by defective renal reabsorption of cystine, ornithine, arginine, and lysine. The increased urinary excretion of cystine results in the development of cystine urolithiasis (CU). The mutated SLC3A1 and SLC7A9 genes are the cause of CU, a global disorder. Its frequency and mutation spectrum vary between different populations. In Asia, the data for CU are limited.

Method: Urinary stones were collected from patients of a single center over a five-year period and analyzed via Fourier transform infrared spectroscopy. Genomic DNA was isolated from 13 patients with CU and their parents and from 26 controls affected by calcium oxalate dihydrate stones. The coding regions and the exon–intron boundaries of SLC3A1 and SLC7A9 were subjected to PCR amplification and then sequenced via traditional Sanger sequencing. Genetic variants were functionally annotated using the InterVar, ClinVar, gnom AD, and HGMD databases.

Results: From the 232 samples of urinary stones, we identified 13 patients with CU (10 males and 3 females). The onset age was from 7 months to 9 years. The CU stones varied from 0.26 cm³ to 18.67 cm³. Sanger sequencing detected a total of 14 SLC3A1 (nine were novel) and 10 SLC7A9 (six were novel) rare variants from the 13 CU families. All variants, including 15 novel variants, were pathogenic, disease-causing, or damaging.

Conclusion: All 13 pediatric CU families harbored SLC3A1 or/and SLC7A9 rare variants. A total of 15 novel pathogenic variants in SLC3A1 and SLC7A9 were identified. This study expanded the known mutational spectrum of CU in the Chinese population.

Keywords: cystine urolithiasis, SLC3A1, SLC7A9, pathogenic variants, Chinese population
BACKGROUND

Urolithiasis, also known as urinary calculi disease, develops when a solid piece of material exists in the urinary tract (Miller and Lingeman, 2007). Most kidney stones form because of a combination of genetics and environmental factors (Miller and Lingeman, 2007). Urolithiasis has serious consequences if not treated immediately. Cystine urolithiasis (CU) is a genetic disorder characterized by defective renal reabsorption of cystine, arginine, lysine, and ornithine; the increased urinary excretion of cystine results in the formation of kidney stones (Eggermann et al., 2012; Fattah et al., 2014). Two genes responsible for cystinuria and CU have been identified: SLC3A1, which encodes the heavy subunit rBAT of the renal b0,+ transporter; and SLC7A9, which encodes b0,+AT, the interacting light subunit of the b0,+ transporter (Calonge et al., 1994; Feliubadaló et al., 1999). b0,+ and b0,+AT combine with each other through disulfide linkage, and only the combined b0,+–b0,+AT heterodimer is functional (Chillarón et al., 2010). The inheritance for cystinuria may vary from autosomal recessive (AR) to autosomal dominant (AD) with incomplete penetrance to digenic pattern (Dello Strologo et al., 2002; Sahota et al., 2019). Accordingly, cystinuria is divided into the following subtypes: biallelic SLC3A1 mutations (AA genotype), biallelic SLC7A9 mutations (BB genotype), a single heterozygous SLC3A1 mutation (A genotype), a single heterozygous SLC7A9 mutation (B genotype), and a single heterozygous SLC3A1 mutation combined with a single heterozygous SLC7A9 mutation (AB genotype) (Dello Strologo et al., 2002; Sahota et al., 2019).

Cystinuria is a global disease with a population-specific prevalence (Eggermann et al., 2012). Although the overall frequency is estimated at 1:7,000 in neonates (Segal and Thier, 1995), the frequency varies in different areas. The rate of CU is 1:2,500 in Libyan Jews, 1:15,000 in Americans, and 1:100,000 in Swedes (Weinberger et al., 1974; Segal and Thier, 1995). In Libyan Jews, the mutant gene carrier rate is as high as 1:25 (Weinberger et al., 1974). In Sweden, 0.5% of the general population carries the SLC3A1 p.Met467Thr variant (Harnevik et al., 2001; Harnevik et al., 2003). In Asia, cystinuria is rarely reported and its frequency in the Chinese population is unclear.

In this study, we analyzed the composition of 232 samples of kidney stones and subjected 13 cases of childhood CU to genetic analysis. A total of 24 pathogenic variants in SLC3A1 and SLC7A9 were detected, 15 of which were novel. These data expanded the spectrum of CU variants in the Chinese population.

METHODS

Criteria for Pediatric CU and the Controls

Data from pediatric CU patients were collected from 2012 to 2017. A total of 13 CU patients were enrolled in this study (Supplementary Data 1). Patients were diagnosed with pediatric CU if (i) they were aged 0–18 years old, (ii) passed visible urinary stones under a clinical setting, and (iii) passed pure or cystine stones as identified via stone composition analysis. The 26 controls were taken from sporadic cases of patients with calcium oxalate dihydrate stones (Supplementary Data 1).

DNA Isolation and Sanger Sequencing

Peripheral blood samples were obtained from 13 Trios-families and 26 sporadic cases of other kidney stones (calcium oxalate dihydrate stones). DNA was extracted using a genomic DNA isolation kit (D3392-02; Omega Bio-Tek, Inc., Norcross, GA, USA) in accordance with a standard protocol. The coding regions and intron–exon junctions of the SLC3A1 and SLC7A9 genes were amplified via PCR by using primers synthesized by BGI, a local biotech company (Shenzhen, China). Primers were designed with Primer3 software (http://frodo.wi.mit.edu). The primer sequences and PCR conditions are provided in Supplementary Table 1. Sanger sequencing was performed on an Applied Biosystems™ 3500 Dx Genetic Analyzer by using a BigDye 3.1 sequencing kit (Applied Biosystems, CA, USA).

Variant Validation

All Sanger sequencing results were compared with the reference SLC3A1 and SLC7A9 sequences (NM_000341 and NM_014270, GRCh37/hg19, http://genome.ucsc.edu/cgi-bin/hgGateway) by applying SEQMAN software (DNA Star Package, Wisconsin, USA). Genetic variants were functionally annotated using InterVar (version 20180118) and screened for reported mutations by using ClinVar (version 20180603) and the HGMD database (public version). We further customized the clinical classification of each variant in accordance with the ACMG/AMP 2015 guidelines by applying automatically interpreted InterVar results and by integrating individualized information, such as family history and inheritance mode, obtained in this study with the results of previous studies.

RESULTS

Clinical Data of 13 Patients With Pediatric CU

A total of 13 patients with CU were identified, 10 of whom were males and 3 were females. These patients originated from 232 patients with urinary stones that we treated from 2002 to 2007. The patients had a mean age of 3.82 ± 3.12 years (range: 0.6–9.3) at first stone onset. The mean stone size of the patient group was 4.12 ± 4.96 cm³ (range: 0.26–18.67). Two urethral (3.77%), 2 bladder (3.77%), 14 ureteral (26.42%), 22 renal pelvic or upper/middle calyceal (41.51%), and 13 lower calyceal (46.43%) calculi were noted. Five children had bilateral calculi, whereas two children had staghorn calculi. Seven children had a family history of CU. Twelve patients had normal initial renal function (serum creatinine [CREA] 20–120 μmol/L, blood urea nitrogen [BUN] 1.8–8.2 mmol/L, and serum uric acid [UA] 90–350 μmol/L). The remaining patient with bilateral ureteral calculi exhibited various degrees of renal dysfunction (625.3, 36.82, and 618.8 μmol/L). The mean number of operations was 3.61 ± 2.14 (range: 1–9), including 11 minimally invasive percutaneous
nephrolithotomy, 10 retrograde intrarenal surgery, and 26 ureteroscopic lithotripsy. The mean stone-free rate was 46.15% after the final operation. Table 1 lists the clinical features of the 13 patients with CU.

Identification of SLC3A1 and SLC7A9 Variants on 24 Alleles via Sanger Sequencing

Sanger sequencing was successfully conducted for the 13 patients with pediatric CU and their parents. After filtering out variants with MAF > 0.01 using the gnomAD database and the variants present in 26 controls, we detected 14 SLC3A1 and 8 SLC7A9 variants on 24 alleles from these 13 families (Table 2, Figures 1–3). These variants covered the whole spectrum of mutations and ranged from insertion, deletion, splicing, and missense variants. Six families presented with biallelic SLC3A1 variants (AA genotype) (Figure 1), and four families exhibited biallelic SLC7A9 variants (BB genotype) (Figure 2). The genotypes of the remaining three families included a single heterozygous SLC3A1 variant (A genotype), a single heterozygous SLC7A9 variant (B genotype), and a single heterozygous SLC3A1 variant combined with a single heterozygous SLC7A9 variant (AB genotype) (Figure 3).

Among these 24 variants, 15 have not been reported elsewhere (9 on SLC3A1, 6 on SLC7A9).

According to the ACMG/AMP 2015 guideline classification (Table 2), five of the nine SLC3A1 variants were pathogenic and four were likely pathogenic; two of the six SLC7A9 variants were pathogenic and another two were likely pathogenic. The classifications of the remaining two variants of SLC7A9 were uncertain. These 15 novel variants included the following: (1) For SLC3A1: c.2011C > T:p.Arg671Ter, c.1326C > G:p.Asn442Lys, c.1304T > G:p.Met435Arg, c.1113C > A:p.Tyr371Ter, c.1365delG:p.Ser455Valfs, c.817T > G:p.Cys273Arg, c.1097A > G:p.Gln366Arg, c.1332+2T > A, and c.2011C > T:p.Arg671Ter. (2) For SLC7A9: c.525delC:p.Tyr175Ter, c.1399+5C > G, c.538_540del:p.180_180del, c.236G > T:p.Gly79Val, c.767T > C:p.Ile256Thr, and exon11:c.1201A > T:p.Lys401Ter.

Further functional effects were tested for all variants via three programs in silico (i.e., REVEL, ClinPred, and MutationTaster). Results showed that 13 of the 15 novel variants were damaging, disease-causing, or pathogenic (Table 3). The remaining two SLC7A9 variants (i.e., c.1399+5C > G and c.538_540del:p.Phe180del) were likely pathogenic. Thus, further confirmatory experiments are needed.

Genotype-Phenotype Correlation for 13 CU Families

The 13 CU families were divided into three groups: classical AR inheritance (six AA and four BB genotypes), AD inheritance (one A and one B genotype), and digenic inheritance (one AB genotype) (Table 4). Several points were observed in this study: (1) SLC3A1 is the main disease gene for childhood CU. SLC3A1 is mutated in 8 out of the 13 patients with CU and the number of

### Table 1 | Clinical features of 13 patients with cystine urolithiasis.

| Characteristics | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 | Patient 10 | Patient 11 | Patient 12 | Patient 13 |
|-----------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Gender          | Male      | Male      | Male      | Male      | Female    | Male      | Male      | Male      | Male      | Male      | Male      | Male      | Female    |
| Age, yr         | 9.3       | 1.7       | 1.8       | 1.0       | 3.1       | 2.8       | 1.5       | 8.3       | 9.3       | 2.9       | 0.6       | 2.8       | 4.6       |
| Initial         | Stone     | Stone     | UTI       | GHU       | Stone     | Stone     | GHU       | Stone     | Stone     | Stone     | Stone     | Stone     |
| presentation    |           |           |           |           |           |           |           |           |           |           |           |           |           |
| Bilateral stones| -         | +         | -         | -         | -         | -         | -         | -         | -         | -         | -         | +         | -         |
| Staghorn stone  | +         | -         | -         | -         | -         | -         | -         | -         | +         | -         | +         | -         | -         |
| Number of stones| 6         | 2         | 3         | 4         | 2         | 2         | 1         | 3         | 2         | 14        | 9         | 2         | 3         |
| Stone size(cm³) | 7.75      | 2.83      | 2.50      | 1.18      | 1.28      | 3.41      | 7.77      | 0.26      | 3.10      | 18.67     | 1.17      | 2.51      | 1.17      |
| Number of operations | 3 | 6 | 1 | 2 | 3 | 3 | 1 | 3 | 9 | 5 | 3 | 4 | 4 |
| MPCNL           | 2         | 3         | 0         | 0         | 0         | 0         | 0         | 0         | 0         | 0         | 0         | 0         | 0         |
| RIRS            | 1         | 0         | 1         | 1         | 1         | 1         | 0         | 1         | 3         | 0         | 0         | 0         | 2         |
| URL             | 2         | 3         | 1         | 1         | 2         | 2         | 1         | 0         | 6         | 1         | 3         | 4         | 2         |
| Family history  | -         | +(Uncle)  | -         | +          | +(Parents) | -         | +         | (Brother) | +          | (Grandfather) | -         | +          | (Great-uncle) |
| Urolithiasis at last follow-up | -         | +         | +         | +         | +         | +         | -         | +         | +         | -         | -         | +         | -         |
| Infant feeding  | Sanlu milk powder | Breast milk supplemented with milk | Breast milk | Breast milk for 2 months, goat’s milk thereafter | Breast milk supplemented with milk | Milk powder | Breast milk | Breast milk | Breast milk | Milk | Breast milk | Milk | Breast milk |
| Comorbidity     | -         | -         | -         | -         | -         | -         | -         | -         | -         | -         | -         | -         | -         |
| Serum calcium   | 2.3       | 2.36      | 2.29      | 2.51      | 2.35      | 2.38      | 2.21      | 2.35      | 2.41      | 2.24      | 2.24      | 2.19      | 2.33      |

Sanlu milk powder was found to contain high levels of melamine. GHU, gross hematuria; MPCNL, minimally invasive percutaneous nephrolithotomy; RIRS, retrograde intrarenal surgery; URL, ureteroscopic lithotripsy.
| Patient | Position | Ref | Alt | Gene | Func.refGene | Exonic Func. | AA Change | HGMD | ACMG interpretation |
|---------|----------|-----|-----|------|-------------|-------------|-----------|------|-------------------|
| 1       | 44528214 | C   | T   | SLC3A1 | exonic | NM_000341 | nonsynonymous SNV | exon6:c.1084C > T: p.Arg362Cys | Pathogenic | Pathogenic (PS1,PM1,PM2,PM3,PP3,PP4) |
| 1       | 44547731 | C   | T   | SLC3A1 | exonic | NM_000341 | stopgain | NA | Pathogenic (PSV1,PM2,PM3,PP3,PP4) |
| 2       | 44531471 | C   | G   | SLC3A1 | exonic | NM_000341 | nonsynonymous SNV | exon7:c.1326C > G: p.Asn442Lys | NA | Likely pathogenic (PM2, PM3,PP4) |
| 2       | 44547360 | C   | T   | SLC3A1 | exonic | NM_000341 | nonsynonymous SNV | exon10:c.1640C > T: p.Ser547Leu | Pathogenic | Pathogenic (PS1,PM1,PM2,PM3,PP3,PP4) |
| 3       | 44531471 | C   | G   | SLC3A1 | exonic | NM_000341 | stopgain | NA | Likely pathogenic (PM2, PM3,PP3,PP4) |
| 3       | 44547360 | C   | T   | SLC3A1 | exonic | NM_000341 | stopgain | NA | Likely pathogenic (PM2, PM3,PP3,PP4) |
| 4       | 44531471 | C   | G   | SLC3A1 | exonic | NM_000341 | nonsynonymous SNV | exon7:c.1304T > G: p.Met435Arg | NA | Likely pathogenic (PM1, PM2,PM3,PP3,PP4) |
| 4       | 44539806 | C   | T   | SLC3A1 | exonic | NM_000341 | nonsynonymous SNV | exon8:c.1414C > T: p.Leu472Phe | Pathogenic | Pathogenic (PS1,PM1,PM2,PM3,PP3,PP4) |
| 5       | 44527229 | G   | A   | SLC3A1 | exonic | NM_000341 | splicing deletion | exon5:c.1012-1G > A: p.Lys401Glu | Pathogenic | Pathogenic (PS1,PM2,PM3,PP3,PP4) |
| 6       | 44531471 | C   | G   | SLC3A1 | exonic | NM_000341 | nonsynonymous SNV | exon8:c.787T > G: p.Leu263Val | Pathogenic | Pathogenic (PSV1,PM2,PM3,PP4) |
| 7       | 44531471 | C   | G   | SLC3A1 | exonic | NM_000341 | nonsynonymous SNV | exon10:c.2011C > T: p.Arg671Ter | NA | Pathogenic (PSV1,PM2,PM3,PP4) |
| 8       | 44531471 | C   | G   | SLC3A1 | exonic | NM_000341 | nonsynonymous SNV | exon8:c.1201A > T: p.Lys401Ter | NA | Pathogenic (PSV1,PM2,PM3,PP4) |
| 9       | 44531471 | C   | G   | SLC3A1 | exonic | NM_000341 | nonsynonymous SNV | exon7:c.1326C > G: p.Asn442Lys | Pathogenic | Pathogenic (PS1,PM1,PM2,PM3,PP3,PP4) |
| 10      | 44531471 | C   | G   | SLC3A1 | exonic | NM_000341 | nonsynonymous SNV | exon10:c.2011C > T: p.Arg671Ter | NA | Pathogenic (PSV1,PM2,PM3,PP4) |
| 11      | 44531471 | C   | G   | SLC3A1 | exonic | NM_000341 | nonsynonymous SNV | exon10:c.2011C > T: p.Arg671Ter | NA | Pathogenic (PSV1,PM2,PM3,PP4) |
| 12      | 44531471 | C   | G   | SLC3A1 | exonic | NM_000341 | nonsynonymous SNV | exon10:c.2011C > T: p.Arg671Ter | NA | Pathogenic (PSV1,PM2,PM3,PP4) |
| 13      | 44531471 | C   | G   | SLC3A1 | exonic | NM_000341 | nonsynonymous SNV | exon10:c.2011C > T: p.Arg671Ter | NA | Pathogenic (PSV1,PM2,PM3,PP4) |

TABLE 2 | Rare variants on SLC3A1 AND SLC7A9 detected in 13 families with cystine urolithiasis.
stones is 2–9 for AA genotype and 1–3 for BB genotype. (2) Patients with AD inheritance had the highest number of stones. In family number 10 with A genotype, the number of stones is 14. In family number 11 with B genotype, the number of stones is 9. (3) Childhood CU may represent a more aggressive form. By contrast, the pathogenic variants in \( SLC3A1 \) or \( SLC7A9 \) (Eggermann et al., 2012) cannot all be detected in cystiruia patients. In this study, we detected the pathogenic variants in \( SLC3A1 \) or \( SLC7A9 \) in all CU patients, suggesting that pediatric CU patients may represent a more aggressive group.

**Phenotypic Details for Three CU Patients With Heterozygous Variants**

Three cases harboring \( SLC3A1 \) or (and) \( SLC7A9 \) heterozygous variants were identified. For patient number 6 with AB genotype, no clinical symptom of urolithiasis was observed during health...
examinations. The patient’s 24-h urinary calcium was 0.42 mmol/L, 24-h urinary phosphorus was 9.75 mmol/L, serum calcium was 2.38 mmol/L, serum phosphate was 1.61 mmol/L, BUN was 3.39 mmol/L, CREA was 18.32 µmol/L, and UA was 269.31 µmol/L. However, the B ultrasound detected stones in the patient’s urinary system.

Patient number 10 with A genotype carried an SLC3A1 spicing variant (c.1012-1G > A) that was previously reported as pathogenic (Saadi et al., 1998). The patient’s initial symptom was dysuria but without urinary frequency and urgency. His 24-h urinary calcium was 0.12 mmol/L, 24-h urinary phosphorus was 7.94 mmol/L, serum calcium was 2.24 mmol/L, serum phosphate was 2.19 mmol/L, BUN was 4.42 mmol/L, CREA was 41.65 µmol/L, and serum UA was 182.91 µmol/L. However, the B ultrasound detected stones in the patient’s urinary system.

Patient number 11 with B genotype carried an SLC7A9 spicing variant (1399 + 2_3insT) that was also previously reported as pathogenic (Yuen et al., 2006). The patient had spontaneous discharge of small stones (at 3 months old) according to his parents. The patient’s 24-h urinary calcium was 0.59 mmol/L, 24-h urinary phosphorus was 3.92 mmol/L, serum calcium was 2.24 mmol/L, serum phosphate was 2.19 mmol/L, BUN was 3.37 mmol/L, CREA was 32.2 µmol/L, and serum-UA was 217.26 µmol/L.

**DISCUSSION**

Cystinuria is a metabolic disease caused by defects in the SLC3A1 and SLC7A9 genes. These gene defects result in decreased renal reabsorption of cystine, ornithine, arginine, and lysine. Most patients with cystinuria develop CU, but the age at onset varies (Harnevik et al., 2003). In this study, we subjected 13 patients with pediatric CU to mutation screening and observed typical SLC3A1 and SLC7A9 pathogenic variants consistent with AA, BB, or AB genotypes in 11 of the families with CU and heterozygous SLC3A1 and SLC7A9 rare variants in two of the families with CU (i.e.,
FIGURE 3 | Rare variants of AB, A or B genotypes in three cystine urolithiasis (CU) families. Solid squares or circles mean the patients were affected by CU. Open squares or circles denote that the patients were not affected by CU.
family numbers 10 and 11). Family numbers 10 and 11 suffer from cystine urolithiasis.

**TABLE 4** | In-brief lists of genotype and phenotype data for 13 families with cystine urolithiasis.

| Inheritance | Genotype | Number of patients | Onset age | Stone size | Stone number |
|-------------|----------|--------------------|-----------|------------|--------------|
| AR          | AA       | 6                  | 1-9.3     | 1.18-7.75  | 2-9          |
|             | BB       | 4                  | 1.5-8.3   | 0.26-1.17  | 1-3          |
| AD          | A        | 1                  | 2.9       | 18.67      | 14           |
|             | B        | 1                  | 0.6       | 1.17       | 9            |
| Digenic     | AB       | 1                  | 2.8       | 3.41       | 2            |

AD, autosomal dominant; AR, autosomal recessive; Onset age: Years; Stone size: cm³.

**CONCLUSIONS**

We detected a total of 24 rare variants in the SLC3A1 and SLC7A9 genes from 13 families with CU. Among these variants, 15 were novel. Functional evaluation analysis confirmed that all these novel variants are pathogenic, damaging, or disease-
causing. These data expanded the spectrum of CU variants in the Chinese population.

DATA AVAILABILITY STATEMENT

The SLC3A1 and SLC7A9 genetic polymorphism data can be found in ClinVar, accession number SUB6699202.

FIGURE 4 | Schematic presentation of SLC3A1 or SLC7A9 pathogenic variants in the Chinese population that have been reported thus far. One dot (at the end of the variants) represents the variants reported by Yuen et al. (2006). Two dots denote the variants reported by Shen et al. (2017). Three dots mean the variants reported by Ma et al. (2018). Red dots are the variants identified in the present study.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Academic Committee of Hunan Children’s Hospital (Approval number: HCHLL58, Changsha City, Hunan Province, China). Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.
AUTHOR CONTRIBUTIONS

Writing of the first draft: CL, YY, YZ, and YwZ. Review and Critique: YY and YwZ. Conception: CL, YY, YwZ. Organization: YY, YZ. Execution: YY, CL, YwZ, YZ. Clinical support: FS, LL, YL, LpL. Material support: YY, YwZ, CL, YZ, YL and LL.

FUNDING

This work was supported by the Natural Science Foundation of Hunan Province, China (2017JJ2139) and Hunan Health Commission Research Fund (B2019019).

REFERENCES

Alirezaee, N., Kernohan, K. D., Hartley, T., Majewski, J., and Hocking, T. D. (2018). ClinPrek prediction tool to identify disease-relevant nonsynonymous single-nucleotide variants. Am. J. Hum. Genet. 103 (4), 474–483. doi: 10.1016/j.ajhg.2018.08.005
Boztenthart, E., Vester, U., Schmidt, C., Hesse, A., Halber, M., Wagner, C., et al. (2002). Cystinuria in children: distribution and frequencies of mutations in the SLC3A1 and SLC7A9 genes. Kidney Int. 62, 1136–1142. doi: 10.1111/j.1523-1755.2002.kid552.x
Calonge, M. J., Gaparini, P., Chillaron, J., Chillon, M., Gallucci, M., Roussaud, F., et al. (1999). Cystinuria caused by mutations in rBAT, a gene involved in the transport of cystine. Nat. Genet. 6, 420–425. doi: 10.1038/ng0494-420
Chillarón, J., Font-Llitjós, M., Fort, J., Zorzano, A., Goldfarb, D. S., Nunes, V., et al. (2010). Pathophysiology and treatment of cystinuria. Nat. Rev. Nephrol. 6, 424–434. doi: 10.1038/nrneph.2010.69
Dello Strologo, L., Pras, E., Pontesilli, C., Beccia, E., Ricci-Barbini, V., de Sanctis, L., et al. (2010). Pathophysiology of cystinuria. J. Am. Soc. Nephrol. 13, 2547–2553. doi: 10.1097/01.ASN.0000392586.17680.E5
Eggermann, T., Venghaus, A., and Zerres, K. (2012). Cystinuria: an inborn cause of urolithiasis. Orphanet J. Rare Dis. 7, 19. doi: 10.1186/1750-1172-7-19
Fattah, H., Hambaroush, Y., and Goldfarb, D. S. (2014). Cystine nephrolithiasis. Transl. Androl. Urol. 3 (3), 228–233. doi: 10.3978/j.issn.2223-4683.2014.07.04
Feliubadaló, L., Font, M., Purroy, J., Roussaud, F., Estivill, X., Nunes, V., et al. (2019). Pathophysiology and treatment of cystinuria. Cystinuria: genetic aspects, mouse models, and a new approach to therapy. Urolithiasis 47, 57–66. doi: 10.1007/s00224-018-1101-7
Harnevik, L., Fjellstedt, E., Molbaek, A., Denneberg, T., and Söderkvist, P. (2003). International cystinuria consortium. Non-type I cystinuria caused by mutations in SLC7A9, encoding a subunit (bo,+AT) of rBAT. Hum. Mutat. 18, 516–525. doi: 10.1002/humu.1228
Harnevik, L., Fjellstedt, E., Molbaek, A., Denneberg, T., and Söderkvist, P. (2003). Cystinuria caused by mutations in the SLC7A9 gene in Swedish cystinuria patients. Hum. Mutat. 18, 516–525. doi: 10.1002/humu.1228
Yuen, Y. P., Lam, C. W., Lai, C. K., Tong, S. F., Li, P. S., Tam, S., et al. (2006). Heterogeneous mutations in the SLC3A1 and SLC7A9 genes in Chinese patients with cystinuria. Kidney Int. 69, 123–128. doi: 10.1038/sj.ki.5000003

CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Li, Yang, Zheng, Shen, Liu, Li, and Zhao. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction which does not comply with these terms.