A novel compound heterozygous mutation in SLC5A2 contributes to familial renal glucosuria in a Chinese family, and a review of the relevant literature

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Abstract. Familial renal glucosuria (FRG) is a rare condition that involves isolated glucosuria despite normal blood glucose levels. Mutations in the solute carrier family 5 member 2 (SLC5A2) gene, which encodes sodium-glucose cotransporter 2 (SGLT2), have been reported to be responsible for the disease. Genetic testing of the SLC5A2 gene was conducted in a Chinese family with FRG. A number of online tools were used to predict the potential effect of the identified mutations on SGLT2 function. Additionally, the SLC5A2 mutations previously reported in PubMed were summarized. A novel compound heterozygous mutation (c.514T>C, p.W172R; c.1540C>T, p.P514S) of the SLC5A2 gene in a Chinese child with FRG was identified. In total, 86 mutations of the SLC5A2 gene have been reported to be associated with FRG. The novel compound heterozygous mutation (c.514T>C, p.W172R; c.1540C>T, p.P514S) of the SLC5A2 gene may be responsible for the onset of FRG. The present study provides a starting point for further investigation of the molecular pathogenesis of the SLC5A2 gene mutation in patients with FRG.

Introduction

Familial renal glucosuria [FRG; Online Mendelian Inheritance in Man (https://www.omim.org) no. 233100] is a hereditary kidney disease characterized by persistent glucosuria due to a reduction in the renal tubular reuptake of glucose, along with normal blood glucose levels and no other impaired tubular functions (1). In general, FRG is a benign condition that does not require any specific therapy. The ability of the kidney to reabsorb glucose principally involves the lower-affinity high-capacity sodium-glucose cotransporter 2 (SGLT2), which is located in the proximal convoluted tubule segment S1 and has a Na⁺-glucose coupling ratio of 1:1 (2). SGLT2 is encoded by the solute carrier family 5 member 2 (SLC5A2) gene and has 672 amino acids. A large number of case reports conducted using patients of different ethnicities have confirmed that SLC5A2 mutations are responsible for the majority of FRG cases (3-22). Variations in the SLC5A2 gene impact the function of SGLT2, leading to isolated glucosuria. However, various different modes of inheritance have been reported for FRG. Notably, research on SGLT2 has been benefitted in recent years by its identification as a therapeutic target in type 2 diabetes mellitus. In the present study, an association between FRG and a novel compound heterozygous mutation of the SLC5A2 gene was identified. Moreover, all the SLC5A2 mutations in patients with FRG that have been reported to date are summarized in the present study. The present study provides additional information on the genetic mechanism of FRG.

Materials and methods

Subject. The subject of the present study was a Han Chinese girl. The patient was observed to exhibit glucosuria in the absence of hyperglycemia at the age of 1 year and 9 months, following an initial urine test. Routine urinary analysis showed glucose in the range + (100 mg/dl) to +++ (500 mg/dl), with no other abnormalities. The quantitative test for urine glucose gave a result of 15.77 g/1.73 m²/24 h. The patient was subjected to an oral glucose tolerance test and exhibited a 2-h postprandial sugar level of 5.1 mmol/l. The patient had no polyuria, polydipsia or polyphagia, and her body weight gain was the same as that of age-matched children. The patient experienced no problems with activity, eating, sleeping or excretory function. There was no reported history of trauma or poisoning. The parents and other family members had no history of glucosuria.

Genetic testing. Following collection of 2 ml blood samples from the parents of the patient, who had no history of FRG, and healthy controls from July to August 2017, genomic DNA
was extracted from the peripheral blood leukocytes using a Wizard genomic DNA purification kit (Promega Corporation, Madison, WI, USA), according to the manufacturer's protocol. A total of fifty healthy controls (28 males and 22 females; average age 38.84±29.78 months) were recruited. Initially, 900 µl of cell lysis solution was added to a sterile 1.5 ml microcentrifuge tube with 300 µl collected blood to separate the leukocytes. All the exons and consensual intronic regions of the SLC5A2 gene were amplified via polymerase chain reaction (PCR) using a Thermal Cycler 9700 (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA). The primers (forward for Exon5, 5’-ACC ACT GCG AGG GTT ATG AT-3’ and reverse for Exon5, 5’-TCC TCACTCACG CCCAGCAT-3'; forward for Exon12, 5’-GTG TTC ATC GTG GTA GTG TCG G-3' and reverse for Exon12, 5’-CCCTCAGTC GAGAAATTCAGG-3’) were designed using Primer Premier 5.0 software (Premier Biosoft International, Palo Alto, CA, USA). The PCRs were conducted in a total volume of 20 µl containing 1.6 µl DNA, 10 µl 2X Taq Master Mix (CWBIO, Beijing, China), 0.8 µl forward primer (Sangon Biotech Co., Ltd., Shanghai, China), 0.8 µl reverse primer (Sangon Biotech Co., Ltd.) and ddH₂O (added to a final volume of 20 µl), with the following thermal cycling conditions: Denaturing at 94°C for 5 min, 35 cycles of denaturing at 94°C for 30 sec, annealing at 57°C for 30 sec and extension at 72°C for 30 sec, followed by extension at 72°C for 10 min. The sequence analysis of the two coding exons of the SLC5A2 gene was performed using an ABI Prism 3130 genetic analyzer (Applied Biosystems; Thermo Fisher Scientific, Inc.). Potential mutations were defined by their exclusion from the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk) and previously reported mutations on PubMed (http://ncbi.nlm.nih.gov/PubMed/). A total of fifty healthy Chinese individuals containing 100 chromosomes were included as controls. A total of three databases, the dbSNP database of the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/snp/), Exome Variant Server (http://evs.gs.washington.edu/EVS) and 1000 Genomes Project (http://www.1000genomes.org/), were used to eliminate single-nucleotide polymorphisms (SNPs). The study was approved by the Institutional Review Board of the Third Xiangya Hospital, Central South University (Changsha, China).

**Homology analysis.** A comparative analysis of multiple amino acid sequences of SGLT2 was performed for different species using the Basic Local Alignment Search Tool (https://blast.ncbi.nlm.nih.gov/Blast.cgi). The aligned reference sequences were *Homo sapiens* (GenBank NP_003032.1), *Pan troglodytes* (XP_003315171.1), *Macaca mulatta* (XP_001113206.1), *Canis lupus* (XP_005621284.1), *Bos taurus* (NP_976236.1), *Mus musculus* (NP_573517.1), *Rattus norvegicus* (NP_072112.2), *Danio rerio* (NP_998091.1) and *Xenopus tropicalis* (XP_002940641.2).

**Pathogenicity prediction.** The functional effects of protein variants were predicted using three online prediction tools, PolyPhen2 (http://genetics.bwh.harvard.edu/pph2/), SIFT (http://sift.jcvi.org) and Mutation Taster (http://www.mutationtaster.org). These online tools predict the pathogenicity of an altered protein based on the number of conserved amino acids and changes in protein structure.
Literature review. All of the literature previously published on the SLC5A2 mutations (between 2002 and 2017) was retrieved from PubMed. The mutation locations and types for the SLC5A2 gene were summarized.

Results

Genetic testing of the SLC5A2 gene. According to the direct sequencing of the SLC5A2 gene from the patient with FRG, a novel 1 bp missense mutation in exon 5 (c.514T>C, p.W172R) and a previously reported 1 bp missense mutation in exon 12 (c.1540C>T, p.P514S) were revealed (Fig. 1A). The father of the patient carried the same p.P514S mutation, while her mother had the same p.W172R mutation (Fig. 1B and C). However, neither of the parents exhibited glycosuria or hyperglycemia, with fasting plasma glucose levels of 4.8 and 3.9 mmol/l. Screening of the SLC5A2 gene in healthy Chinese individuals revealed no mutant alleles in exon 5 or exon 12.
Table II. Literature review of the clinical characteristics and mutational analysis of the solute carrier family 5 member 2 gene in patients with familial renal glucosuria.

| Author, year             | Age, years | Sex | Urine glucose (g/1.73 m²/24 h) | Allele 1     | Allele 2     | Mutation state | (Refs.) |
|--------------------------|------------|-----|--------------------------------|--------------|--------------|----------------|---------|
| van den Heuvel et al, 2002 | 2          | Male | 61.6                         | c.1320G>A    | c.1320G>A    | Homozygous     | (3)     |
| Santer et al, 2003       | -          | -   | 126-162.2                    | c.973-7 del ATGGT | c.973-7 del ATGGT | Homozygous     | (4)     |
| Santer et al, 2003       | -          | -   | 73.6                         | c.814G>A     | c.814G>A     | Homozygous     | (4)     |
| Santer et al, 2003       | -          | -   | 50.6-51.3                    | IVS7+5G>A    | IVS7+5G>A    | Homozygous     | (4)     |
| Santer et al, 2003       | -          | -   | 21.3                         | IVS7+5G>A    | 920T>C       | Compound heterozygous | (4)     |
| Santer et al, 2003       | -          | -   | 28.5                         | IVS7+5G>A    | 920T>C       | Compound heterozygous | (4)     |
| Santer et al, 2003       | -          | -   | 43.0                         | c.1346G>A    | c.1346G>A    | Homozygous     | (4)     |
| Santer et al, 2003       | -          | -   | 68.7                         | c.1320G>A    | c.1320G>A    | Homozygous     | (4)     |
| Santer et al, 2003       | -          | -   | 20.8                         | c.1461-517 del 57 | -              | -              | (4)     |
| Santer et al, 2003       | -          | -   | 0.6                          | c.1951-92 del 42 | WT             | Heterozygous   | (4)     |
| Santer et al, 2003       | -          | -   | 38.8                         | c.1102C>T    | c.1102C>T    | Homozygous     | (4)     |
| Santer et al, 2003       | -          | -   | 2.3-4.5                      | c.506delC    | WT           | Heterozygous   | (4)     |
| Santer et al, 2003       | -          | -   | 0.75                         | IVS7+5G>A    | WT           | Heterozygous   | (4)     |
| Santer et al, 2003       | -          | -   | 14.6                         | IVS7+5G>A    | 932A>G       | Compound heterozygous | (4)     |
| Santer et al, 2003       | -          | -   | 5.9                          | c.216C>A     | WT           | Heterozygous   | (4)     |
| Santer et al, 2003       | -          | -   | 2.8                          | WT           | WT           | Homozygous     | (4)     |
| Santer et al, 2003       | -          | -   | 202                          | c.410G>A     | c.1152-63 del 12 | Compound heterozygous | (4)     |
| Santer et al, 2003       | -          | -   | 79.8                         | c.1152-63 del 12 | c.1152-63 del 12 | Compound heterozygous | (4)     |
| Santer et al, 2003       | -          | -   | 1.8                          | c.151A>C     | WT           | Homozygous     | (4)     |
| Santer et al, 2003       | -          | -   | 30.1-92.4                    | c.1627A>C    | c.1627A>C    | Homozygous     | (4)     |
| Santer et al, 2003       | -          | -   | 4.8                          | c.313G>A     | WT           | Heterozygous   | (4)     |
| Santer et al, 2003       | -          | -   | 8.0-16.7                     | WT           | WT           | Homozygous     | (4)     |
| Santer et al, 2003       | -          | -   | 31.7                         | c.448T>C     | c.1495C>T    | Compound heterozygous | (4)     |
| Santer et al, 2003       | -          | -   | 1.2                          | c.1359C>A    | WT           | Heterozygous   | (4)     |
| Santer et al, 2003       | -          | -   | 1.9                          | c.1152-63 del 12 | c.1152-63 del 12 | Compound heterozygous | (4)     |
| Santer et al, 2003       | -          | -   | 0.75                         | IVS7+5G>A    | WT           | Heterozygous   | (4)     |
| Calado et al, 2004       | 41         | Male | 12                           | c.500delA    | c.1961A>G    | Compound heterozygous | (5)     |
| Kleta et al, 2004        | 19         | Female | 9.1                          | c.599C>A     | c.1961A>G    | Compound heterozygous | (6)     |
| Francis et al, 2004      | 82         | Female | >30                          | c.G910A+G911A | c.G910A+G911A | Homozygous     | (7)     |
| Magen et al, 2005        | 3          | Male  | 83                           | c.962A>G     | c.962A>G     | Homozygous     | (8)     |
| Author, year  | Age, years | Sex | Urine glucose (g/1.73 m$^2$/24 h) | Allele 1     | Allele 2     | Mutation state   | (Refs.) |
|--------------|------------|-----|----------------------------------|--------------|--------------|------------------|--------|
| Magen et al., 2005 | 1.5  | Female | 101 | c.962A>G | c.962A>G | Homozygous | (8)   |
| Magen et al., 2005 | 0.2  | Male    | 95  | c.962A>G | c.962A>G | Homozygous | (8)   |
| Magen et al., 2005 | 0.5  | Male    | 114 | c.962A>G | c.962A>G | Homozygous | (8)   |
| Magen et al., 2005 | 1    | Female | 124 | c.962A>G | c.962A>G | Homozygous | (8)   |
| Magen et al., 2005 | 9    | Male    | 169 | c.962A>G | c.962A>G | Homozygous | (8)   |
| Calado et al., 2006 | 50   | -      | 7.6 | c.500delA | WT       | Heterozygous | (9)   |
| Calado et al., 2006 | 40   | -      | 11.6 | IVS12+1G>A | WT       | Heterozygous | (9)   |
| Calado et al., 2006 | 8    | -      | 6.4 | IVS12+1G>A | IVS12+1G>A | Homozygous | (9)   |
| Calado et al., 2006 | 3    | -      | 12.2 | IVS12+1G>A | IVS12+1G>A | Homozygous | (9)   |
| Calado et al., 2006 | 1    | -      | 6.2 | c.395G>A | c.655G>A | Compound heterozygous | (9)   |
| Calado et al., 2006 | 6    | -      | 12.1 | WT       | WT       | Heterozygous | (9)   |
| Calado et al., 2006 | 26   | -      | 65.6 | c.305C>T | c.305C>T | Homozygous | (9)   |
| Calado et al., 2008 | 21   | Male    | 3.2 | c.346G>A | WT       | Heterozygous | (10)  |
| Calado et al., 2008 | 48   | Male    | 6.1  | c.1672C>T | WT       | Heterozygous | (10)  |
| Calado et al., 2008 | 28   | Female | 2.7  | c.1961A>G | WT       | Heterozygous | (10)  |
| Calado et al., 2008 | 6    | Male    | 62.3 | IVS7+5G>A | IVS7+5G>A | Homozygous | (10)  |
| Calado et al., 2008 | 24   | Female | 86.5 | c.670G>C | c.670G>C | Homozygous | (10)  |
| Calado et al., 2008 | 42   | Female | 30   | c.131T>A | c.1145T>C | Compound heterozygous | (10)  |
| Calado et al., 2008 | 14   | Female | 61.1 | c.601G>A | c.1159C>A | Compound heterozygous | (10)  |
| Calado et al., 2008 | 33   | Male    | n.q. | c.968C>G | c.1961A>G | Compound heterozygous | (10)  |
| Calado et al., 2008 | 1.5  | Male    | 35.5 | c.1102C>T | c.1359C>A | Compound heterozygous | (10)  |
| Calado et al., 2008 | 8    | Female | n.q. | IVS7+5G>A | c.1428C>G | Compound heterozygous | (10)  |
| Calado et al., 2008 | 66   | Female | 10   | c.1446G>C | c.1961A>G | Compound heterozygous | (10)  |
| Calado et al., 2008 | 16   | Female | 6.5  | c.898C>T | WT       | Heterozygous | (10)  |
| Calado et al., 2008 | 8    | Male    | n.q. | IVS7+5G>A | IVS7+5G>A | Homozygous | (10)  |
| Calado et al., 2008 | 5    | Female | n.q. | IVS7+5G>A | IVS7+5G>A | Homozygous | (10)  |
| Calado et al., 2008 | 12   | Male    | 15.2 | c.1616T>C | c.1616T>C | Homozygous | (10)  |
| Calado et al., 2008 | 9    | Male    | 23.1 | c.1616T>C | c.1616T>C | Homozygous | (10)  |
| Calado et al., 2008 | 2    | Female | 14.2 | IVS7+5G>A | c.1405G>A | Compound heterozygous | (10)  |
| Calado et al., 2008 | 16   | Female | 66.9 | c.1068G>A | IVS12+1G>A | Compound heterozygous | (10)  |
Table II. Continued.

| Author, year | Age, years | Sex | Urine glucose (g/1.73 m²/24 h) | Allele 1 | Allele 2 | Mutation state | (Refs.) |
|--------------|------------|-----|---------------------------------|----------|----------|----------------|--------|
| Calado et al, 2008 | 12 | Female | 72.7 | c.384C>G | c.384C>G | Homozygous | (10) |
| Yu et al, 2011 | 36 | Female | 16.06 | IVS11+1G>C | IVS1-16C>A | Compound heterozygous | (11) |
| Yu et al, 2011 | 27 | Male | 6.47 | c.294C>A | WT | Heterozygous | (11) |
| Yu et al, 2011 | 41 | Female | 6.30 | c.1388T>G | WT | Heterozygous | (11) |
| Yu et al, 2011 | 15 | Female | 27 | IVS1-16C>A | c.1345C>G | Compound heterozygous | (11) |
| Lee et al, 2012 | - | Male | 46.6 | c.1435C>G, c.1346G>A | WT | Compound heterozygous | (12) |
| Lee et al, 2012 | - | Male | 18.3 | c.979C>T | c.1499T>G | Compound heterozygous | (12) |
| Lee et al, 2012 | - | Female | 22.0 | c.736C>T | c.1499T>G | Compound heterozygous | (12) |
| Lee et al, 2012 | - | Male | 15.3 | c.1346G>A | c.1346G>A | Homozygous | (12) |
| Lee et al, 2012 | - | Female | 76.8 | c.409C>T | c.1732C>T | Compound heterozygous | (12) |
| Lee et al, 2012 | - | Male | 32.7 | c.983T>G | c.1894_1895ins6 | Compound heterozygous | (12) |
| Lee et al, 2012 | - | Male | 42.6 | c.1382G>A | c.1540C>T | Compound heterozygous | (12) |
| Lee et al, 2012 | - | Male | 24.9 | c.1346G>A | WT | Heterozygous | (12) |
| Lee et al, 2012 | - | Male | 12.1 | c.867G>C | WT | Heterozygous | (12) |
| Lee et al, 2012 | - | Female | 35.2 | c.1346G>A | WT | Heterozygous | (12) |
| Lee et al, 2012 | - | Male | 30.9 | c.1798delC | WT | Heterozygous | (12) |
| Lee et al, 2012 | - | Female | 8.9 | c.320T>C | WT | Heterozygous | (12) |
| Lee et al, 2012 | - | Male | 33.7 | c.938G>A | WT | Heterozygous | (12) |
| Lee et al, 2012 | - | Male | 16.2 | c.1346G>A | WT | Heterozygous | (12) |
| Lee et al, 2012 | - | Male | 6.9 | c.1507G>A | WT | Heterozygous | (12) |
| Lee et al, 2012 | - | Female | 5.1 | c.1540C>T | WT | Heterozygous | (12) |
| Lee et al, 2012 | - | Male | 25.2 | c.1418_1432dup15 | WT | Heterozygous | (12) |
| Lee et al, 2012 | - | Female | 1.9 | c.1357T>A | WT | Heterozygous | (12) |
| Lee et al, 2012 | - | Female | 15.5 | c.1346G>A | WT | Heterozygous | (12) |
| Lee et al, 2012 | - | Male | 4.7 | c.170T>C | WT | Heterozygous | (12) |
| Lee, 2013 | 40 | Male | 10.8 | c.1162del1G | WT | Heterozygous | (13) |
| Yu et al, 2014 | 50 | Male | 4.8 | c.229G>C | WT | Heterozygous | (14) |
| Author, year          | Age, years<sup>a</sup> | Sex  | Urine glucose (g/1.73 m<sup>2</sup>/24 h) | Allele 1 | Allele 2 | Mutation state (Refs.) |
|-----------------------|-------------------------|------|-----------------------------------------|----------|----------|-------------------------|
| Lee, 2013             | 40                      | Male | 10.8                                    | c.1162delG | WT       | Heterozygous (13)       |
| Yu et al, 2015        | 36                      | Female | 12.9                                  | c.294C>A   | WT       | Heterozygous (15)       |
| Yu et al, 2015        | 27                      | Male | 19.6                                    | c.736C>T   | c.1420G>C | Compound heterozygous (15) |
| Yu et al, 2015        | 20                      | Male | 5.9                                     | c.1051T>C  | WT       | Heterozygous (15)       |
| Yu et al, 2015        | 58                      | Male | 7.3                                     | c.1400T>C  | WT       | Heterozygous (15)       |
| Yu et al, 2015        | 61                      | Male | 8.1                                     | c.1691G>A  | WT       | Heterozygous (15)       |
| Dhayat et al, 2016    | 70.3                    | Female | 6.71                                  | c.265G>A   | WT       | Heterozygous (16)       |
| Dhayat et al, 2016    | 65.3                    | Female | 11.77                                 | c.265G>A   | WT       | Heterozygous (16)       |
| Dhayat et al, 2016    | 61.8                    | Female | 5.54                                  | c.265G>A   | WT       | Heterozygous (16)       |
| Dhayat et al, 2016    | 40.2                    | Female | 6.53                                  | c.265G>A   | WT       | Heterozygous (16)       |
| Dhayat et al, 2016    | 27.1                    | Male | 1.10                                   | c.265G>A   | WT       | Heterozygous (16)       |
| Ottosson-Laakso et al, 2016 | -                | Female | 55.2                                 | c.300-303+2del | -       | Compound heterozygous (17) |
| Yu et al, 2016        | 39                      | Female | 7.56                                  | c.1891G>A  | WT       | Heterozygous (18)       |
| Yu et al, 2016        | 36                      | Female | 8.3                                   | c.1319G>A  | WT       | Heterozygous (19)       |
| Zhao et al, 2016      | 22                      | Male | 10.56                                  | c.1003A>G  | c.1343A>G + c.1739G>A  | Compound heterozygous (20) |
| Zhao et al, 2016      | 26                      | Male | 1.96                                   | c.886(-10₋31)del | WT  | Heterozygous (20)       |
| Zhao et al, 2016      | 30                      | Male | 1.77                                   | c.886(-10₋31)del | WT  | Heterozygous (20)       |
| Zhao et al, 2016      | 32                      | Female | 1.66                                 | c.886(-10₋31)del | WT  | Heterozygous (20)       |
| Zhao et al, 2016      | 25                      | Male | 12.74                                  | c.886(-10₋31)del | WT  | Heterozygous (20)       |
| Zhao et al, 2016      | 52                      | Male | 1.34                                   | c.1420G>C  | WT       | Heterozygous (20)       |
| Zhao et al, 2016      | 38                      | Male | 50.68                                  | c.886(-10₋31)del + c.886(-10₋31)del | Compound heterozygous (20) |
| Zhao et al, 2016      | 48                      | Female | 1.78                                 | c.393G>C   | WT       | Heterozygous (20)       |
| Kim et al, 2016       | 26                      | Male | 3.7                                    | c.395G>A   | WT       | Heterozygous (21)       |
| Wang et al, 2017      | 24                      | Female | 8.06                                 | c.877A>T   | WT       | Heterozygous (22)       |
| Wang et al, 2017      | 4                       | Female | 10.96                                | c.229G>C   | c.1540C>T | Compound heterozygous (22) |
| 1.75                  | Female | 15.77                                  | c.514T>C   | c.1540C>T | Compound heterozygous | - |

<sup>a</sup>At the time of evaluation; <sup>b</sup>the level of urine glucose was only available in g/l; <sup>c</sup>spot urine glucose/creatinine ratio (mg/mg); <sup>d</sup>the present study. WT, wild type; n.q., persistent glucosuria not quantified.
among 100 screened chromosomes. The novel p.W172R mutation was not identified in the three SNP databases used in the present study.

**Functional prediction of the SLC5A2 mutations.** The results of a comparative analysis of multiple amino acid sequences revealed that the p.W172R and p.P514S variants occurred in highly conserved locations. In addition, the amino acid residues adjacent to the p.W172R and p.P514S variants were also highly conserved among a number of species (Fig. 2). The results of the online analysis performed using PolyPhen-2, SIFT, and Mutation Taster demonstrated that the mutations p.W172R and p.P514S may be deleterious and may be associated with FRG (Fig. 3; Table I).

**Results of the literature review.** To date, 115 index cases of FRG, including the proband assessed in the present study, have been retrieved in total (Table II). The age of patients upon diagnosis with FRG via an initial urine test is between 2 months and 82 years. Among the 83 cases for which the sex was identified, the male-to-female ratio was 1.8±1. The mutation states are heterozygous, homozygous and compound heterozygous. In summary, 86 mutations of the SLC5A2 gene, including one containing the novel mutation p.W172R in the present study, throughout exons 2-14 and the flanking intronic regions, have been reported to be associated with FRG in patients of different ethnicities (Table III). The three most common mutation sites are located in exon 11 (16/86=18.60%), exon 8 (11/86=12.79%) and exon 4 (10/86=11.63%). The mutations are primarily missense (65/86=75.58%), frameshift (7/86=8.14%), splicing (5/86=5.81%), and nonsense (4/86=4.65%) mutations. Chinese and Korean patients in the East Asian region account for 44.31% (39/88) of all reported mutations.

**Discussion**

FRG is an isolated disorder of glucose transport in the proximal tubule with normal glucose metabolism, and may occur in any age groups. The disease has not been reported to occur at any increased frequency in either males or females. The prevalence of FRG has been suggested to be 0.2% in the general Caucasian population (23), while it is suspected to have a prevalence of <0.1% in Japanese schoolchildren (24). FRG is classified into three types (A, B and O) according to urinary glucose levels (25). Severe FRG (glucosuria ≥10 g/l/1.73 m²/24 h), termed type O FRG, is a rare subtype. Patients with type A FRG are characterized by a low renal threshold for glucose and low maximum tubular glucose reabsorption. Those with type B have a low threshold but normal maximum tubular glucose reabsorption. By contrast, patients with type O have a complete absence of renal glucose transport (25). In the majority of affected individuals, the condition causes no apparent symptoms or serious effects associated with the excessive urinary excretion of glucose, such as polyuria or enuresis. However, polyuria, enuresis and a mild delay in growth are reported in patients with type O FRG (26). Various other manifestations, such as episodic dehydration and starvation ketosis, and an increased incidence of urinary tract or genital infection, have also been observed in cases of severe FRG (25). Collectively, kidney biopsies in patients with FRG indicate normal kidney tissue via light microscopy, immunofluorescence and electron microscopy (14).

As the member of the sodium glucose cotransporter family, SGLT2 is primarily expressed in the kidney and helps to maintain ~90% glomerular filtration during glucose reabsorption (27). The SLC5A2 gene is localized in chromosome 16p11.2, with 14 exons, and encodes SGLT2, which contains 672 amino acids. Previous studies have revealed that SLC5A2 mutations are closely associated with the occurrence of FRG (3-22). FRG is primarily caused by mutations in the SLC5A2 gene, which are responsible for the majority of cases. Regarding inheritance patterns, FRG may be inherited in an autosomal recessive or autosomal dominant pattern. However, studies have demonstrated that the inheritance of FRG may best be described as co-dominant with incomplete penetrance (4,22). Previous studies have suggested that patients with heterozygous SLC5A2 mutations are likely to exhibit mild glucosuria (glucosuria ≤10 g/l/1.73 m²/24 h), while homozygous or compound heterozygous mutations tend to lead to severe glucosuria (4,8,12). Not all individuals with heterozygous SLC5A2 variants exhibit glucosuria; this highlights the issue of penetrance (28). Penetrance is difficult to determine reliably, even for genetic diseases that are caused by a single polymorphic allele. For many hereditary diseases, the onset of symptoms is age-associated and affected by environmental factors, such as diet and climate, in addition to genetic cofactors and the epigenetic regulation of expression (29). Specifically, a diagnosis of FRG depends on the detection of urine glucose levels, thus it may be missed due to alterations in the urine glucose level. For example, the urine glucose level will be impacted by the amount of sugar consumed recently.

In the present study, two missense mutations in the SLC5A2 gene of a Chinese patient with FRG accompanied by benign clinical symptoms were reported, one of which was a novel missense mutation (c.514T>C; p.W172R). A total of two previous studies reported that the p.P514S mutation led to FRG with single heterozygous or compound heterozygous status (p.G77R, p.P514S; p.V477G, p.P514S) (12,22). The parents of the proband in the present study carried missense mutations at different locations in terms of SLC5A2 cDNA position, but neither of them had history of glucosuria. Nevertheless, the patient, with p.W172R and p.P514S missense mutations, exhibited severe glucosuria. It is possible that wild-type SGLT2 may serve a compensatory role during the occurrence of FRG caused by SLC5A2 mutations. These results indicated that the inheritance patterns of FRG are best described as co-dominant. Therefore, it may be surmised that the p.W172R and p.P514S compound heterozygous mutation of the SLC5A2 gene contributes to FRG.

SGLT2 has 14 transmembrane helices (TMHs) with the hydrophobic N- and C-terminal domains lying in the extracellular space and contains a sodium solute symporter domain (http://smart.embl-heidelberg.de/; TMHMM server V.2.0). An earlier study on the transport mechanisms of the SGLT1/SGLT2 chimera indicated that the C-terminal domain determined sugar affinity and selectivity (30). p.W172 and p.P514 are localized in the extracellular loops between TMH 4 and TMH 5, and between TMH 12 and 13, respectively (Fig. 4). p.W172 and p.P514 residues were identified to be highly conserved among numerous other species. Meanwhile,
Table III. Literature review of solute carrier family 5 member 2 gene mutations of patients with familial renal glucosuria.

| Author, year            | Site        | Ethnicity  | Nucleotide change | Amino acid change | Mutation type (Refs.) |
|-------------------------|-------------|------------|-------------------|-------------------|-----------------------|
| Yu et al, 2011          | Intron 1    | Chinese    | IVS1-16C>A        | -                 | Splicing (11)         |
| Calado et al, 2008      | Exon 2      | American   | c.131T>A          | p.M44K            | Missense (10)         |
| Santer et al, 2003      | Exon 2      | NA         | c.151A>C          | p.T51P            | Missense (4)          |
| Lee et al, 2012         | Exon 2      | Korean     | c.170T>C          | p.L57P            | Missense (12)         |
| Santer et al, 2003      | Exon 3      | NA         | c.216C>A          | p.F72L            | Missense (4)          |
| Yu et al, 2014; Wang et al, 2017 | Exon 3 | Chinese  | c.229G>C        | p.G77R            | Missense (14,22)      |
| Dhayat et al, 2016      | Exon 3      | Swiss      | c.265G>A          | p.A89T            | Missense (16)         |
| Yu et al, 2011; Yu et al, 2015 | Exon 3 | Chinese  | c.294C>A        | p.F98L            | Missense (11,15)      |
| Laakso et al, 2016      | Exon 3      | Finnish    | c.300-303+2del    | -                 | Frameshift (17)       |
| Calado et al, 2006      | Exon 4      | Turkish    | c.305C>T          | p.A102V           | Missense (9)          |
| Santer et al, 2003      | Exon 4      | NA         | c.313G>A          | p.V105M           | Missense (4)          |
| Lee et al, 2012         | Exon 4      | Korean     | c.320T>C          | p.L107P           | Missense (12)         |
| Calado et al, 2008      | Exon 4      | Portuguese | c.346G>A         | p.V116M           | Missense (10)         |
| Calado et al, 2008      | Exon 4      | Turkish    | c.384C>G          | p.Y128X           | Nonsense (10)         |
| Zhao et al, 2016        | Exon 4      | Chinese    | c.393G>C          | p.K131N           | Missense (20)         |
| Calado et al, 2006; Kim et al, 2016 | Exon 4 | Korean, Turkish | c.395G>A          | p.R132H           | Missense (9,21)       |
| Lee et al, 2012         | Exon 4      | Korean     | c.409C>T          | p.R137C           | Missense (12)         |
| Santer et al, 2003      | Exon 4      | German     | c.410G>A          | p.R137H           | Missense (4)          |
| Santer et al, 2003      | Exon 4      | NA         | c.448T>C          | p.Y150H           | Missense (4)          |
| Santer et al, 2003; Calado et al, 2004; Calado et al, 2006 | Exon 5 | Portuguese, NA | c.500delA | p.Q167fsX186    | Frameshift (4,5,9)    |
| Santer et al, 2003      | Exon 5      | NA         | c.506delC         | p.Q168fs...186X   | Frameshift (4)        |
| Calado et al, 2008      | Exon 6      | Belgian    | c.601G>A          | p.D201N           | Missense (10)         |
| Calado et al, 2006      | Exon 6      | Turkish    | c.655G>A          | p.A219T           | Missense (9)          |
| Calado et al, 2008      | Exon 7      | Belgian    | c.670G>C          | p.G224R           | Missense (10)         |
| Lee et al, 2012; Yu et al, 2015 | Exon 7 | Korean, Chinese | c.736C>T | p.P246S           | Missense (12,15)      |
| Santer et al, 2003      | Exon 7      | NA         | c.814G>A          | p.G272R           | Missense (4)          |
| Lee et al, 2012         | Exon 7      | Korean     | c.867G>C          | p.W289C           | Missense (12)         |
| Wang et al, 2017        | Exon 7      | Chinese    | c.877A>T          | p.S293C           | Missense (22)         |
| Author, year              | Site          | Ethnicity                                           | Nucleotide change | Amino acid change | Mutation type | (Refs.) |
|--------------------------|---------------|----------------------------------------------------|-------------------|-------------------|--------------|---------|
| Santer et al, 2003; Calado et al, 2008 | Intron 7 | Pakistani, former Yugoslav, Italian, Swiss, Canadian, German, Turkish, Macedonian | IVS7+5G>A         | -                 | Splicing     | (4,10)  |
| Zhao et al, 2016         | Intron 7     | Chinese                                            | c.886(-10_−31)del | -                 | Splicing     | (20)    |
| Calado et al, 2008       | Exon 8       | German                                             | c.898C>T          | p.R300C           | Missense     | (10)    |
| Francis et al, 2004      | Exon 8       | Italian                                            | c.G910A+G911A     | p.G304K           | Missense     | (7)     |
| Santer et al, 2003       | Exon 8       | NA                                                 | c.920T>C          | p.L307P           | Missense     | (4)     |
| Santer et al, 2003       | Exon 8       | NA                                                 | c.932A>G          | p.K311R           | Missense     | (4)     |
| Lee et al, 2012          | Exon 8       | Korean                                             | c.938G>A          | p.G313D           | Missense     | (12)    |
| Magen et al, 2005        | Exon 8       | Israeli-Arab descent                               | c.962A>G          | p.K321R           | Missense     | (8)     |
| Calado et al, 2008       | Exon 8       | Belgian                                            | c.968C>G          | p.T323R           | Missense     | (10)    |
| Santer et al, 2003       | Exon 8       | German                                             | c.973–7 del ATGTT  | p.P324fs…347X     | Frameshift   | (4)     |
| Lee et al, 2012          | Exon 8       | Korean                                             | c.979C>T          | p.L327F           | Missense     | (12)    |
| Lee et al, 2012          | Exon 8       | Korean                                             | c.983T>G          | p.M328R           | Missense     | (12)    |
| Zhao et al, 2016         | Exon 8       | Chinese                                            | c.1003A>G         | p.S335G           | Missense     | (20)    |
| Laakso et al, 2016       | Exon 9       | Finnish                                            | c.1051T>C         | p.C351R           | Missense     | (15)    |
| Yu et al, 2015           | Exon 9       | Chinese                                            | c.1051T>C         | p.C351R           | Missense     | (15)    |
| Calado et al, 2008       | Exon 9       | Macedonian                                         | c.1068G>A         | p.G356S           | Missense     | (10)    |
| Santer et al, 2003; Calado et al, 2008 | Exon 9 | NA, Greek                                          | c.1102C>T         | p.R368W           | Missense     | (4,10)  |
| Calado et al, 2008       | Exon 10      | American                                           | c.1145T>C         | p.M382T           | Missense     | (10)    |
| Calado et al, 2008       | Exon 10      | Brazilian                                          | c.1159C>A         | p.L387M           | Missense     | (10)    |
| Lee et al, 2013          | Exon 10      | Korean                                             | c.1162delG        | p.A388fsX48       | Frameshift   | (13)    |
| Santer et al, 2003       | Exon 10      | German                                             | c.1152–63 del 12  | Δ385–8            | Deletion     | (4)     |
| Yu et al, 2016           | Exon 11      | Chinese                                            | c.1319G>A         | p.W440X           | Nonsense     | (19)    |
| van den Heuvel et al, 2002; Santer et al, 2003; Yu et al, 2016 | Exon 11 | Chinese, Turkish                                    | c.1320G>A         | p.W440X           | Nonsense     | (3,4,19)|
| Zhao et al, 2016         | Exon 11      | Chinese                                            | c.1343A>G         | p.Q448R           | Missense     | (20)    |
| Santer et al, 2003; Lee et al, 2012 | Exon 11 | Korean, NA                                          | c.1346G>A         | p.G449D           | Missense     | (4,12)  |
| Lee et al, 2012          | Exon 11      | Korean                                             | c.1357T>A         | p.F453I           | Missense     | (12)    |
| Santer et al, 2003; Calado et al, 2008 | Exon 11 | NA, Greek                                          | c.1359C>A         | p.F453L           | Missense     | (4,10)  |
| Lee et al, 2012          | Exon 11      | Korean                                             | c.1382G>A         | p.S461N           | Missense     | (12)    |
| Author, year | Site       | Ethnicity       | Nucleotide change | Amino acid change | Mutation type (Refs.) |
|------------|------------|-----------------|-------------------|-------------------|-----------------------|
| Yu et al., 2011 | Exon 11    | Chinese         | c.1388T>G         | p.L463R           | Missense (11)         |
| Yu et al., 2015 | Exon 11    | Chinese         | c.1400T>C         | p.V467A           | Missense (15)         |
| Calado et al., 2008 | Exon 11    | Macedonian      | c.1405G>A         | p.A469T           | Missense (10)         |
| Lee et al., 2012 | Exon 11    | Korean          | c.1418_1432dup15  | p.473_477dupLALFV  | Duplication (12)      |
| Yu et al., 2015; Zhao et al., 2016 | Exon 11    | Chinese         | c.1420G>C         | p.A474P           | Missense (15,20)      |
| Calado et al., 2008 | Exon 11    | German          | c.1428C>G         | p.F476L           | Missense (10)         |
| Lee et al., 2012 | Exon 11    | Korean          | c.1430T>G         | p.V477G           | Missense (12)         |
| Yu et al., 2011; Lee et al., 2012 | Exon 11    | Chinese, Korean | c.1435C>G         | p.R479G           | Missense (11,12)      |
| Calado et al., 2008 | Exon 11    | Swiss           | c.1446G>C         | p.E482D           | Missense (10)         |
| Yu et al., 2011 | Intron 11  | Chinese         | IVS11+1G>C        | -                 | Splicing (11)         |
| Santer et al., 2003 | Exon 12   | NA              | c.1461-517 del 57 | p.W487, Δ488-506  | Deletion (4)          |
| Lee et al., 2012 | Exon 12    | Korean          | c.1475_1476insC   | p.L493Pfs*74      | Frameshift (12)       |
| Santer et al., 2003 | Exon 12    | NA              | c.1495C>T         | p.R499C           | Missense (4)          |
| Lee et al., 2012 | Exon 12    | Korean          | c.1499T>G         | p.L499C           | Missense (12)         |
| Lee et al., 2012 | Exon 12    | Korean          | c.1507G>A         | p.E503K           | Missense (12)         |
| Lee et al., 2012; Wang et al., 2017 | Exon 12    | Korean, Chinese | c.1540C>T         | p.S514S           | Missense (12,22)*     |
| Calado et al., 2008 | Exon 12    | Romanian        | c.1616T>C         | p.L539P           | Missense (10)         |
| Santer et al., 2003 | Exon 12    | NA              | c.1627A>C         | p.T543P           | Missense (4)          |
| Calado et al., 2006; Calado et al., 2008 | Intron 12  | Turkish, Macedonian | IVS12+1G>A | -                 | Splicing (9,10)       |
| Calado et al., 2008 | Exon 13    | Portuguese      | c.1672C>T         | p.R558C           | Missense (10)         |
| Yu et al., 2015 | Exon 13    | Chinese         | c.1691G>A         | p.R564Q           | Missense (15)         |
| Lee et al., 2012 | Exon 13    | Korean          | c.1732C>T         | p.Q578*           | Nonse (12)            |
| Zhao et al., 2016 | Exon 13    | Chinese         | c.1739G>A         | p.G580D           | Missense (20)         |
| Lee et al., 2012 | Exon 14    | Korean          | c.1798delC        | p.Q600Rfs*18      | Frameshift (12)       |
| Yu et al., 2016 | Exon 14    | Chinese         | c.1891G>A         | p.E631K           | Missense (18)         |
| Lee et al., 2012 | Exon 14    | Korean          | c.1894_1895ins6   | p.[A634E; 634_635ins2] | Insertion (12)       |
| Santer et al., 2003 | Exon 14    | NA              | c.1951-92 del 42  | Δ651-64           | Deletion (4)          |
| Calado et al., 2004; Kleta et al., 2004; Calado et al., 2008 | Exon 14    | Portuguese, Belgian, Swiss, Russian/Cuban/Spanish ancestry | c.1961A>G         | p.N654S           | Missense (5,6,10)     |

*The present study. NA, not available; the patients were from Germany, Switzerland, England, Italy, former Yugoslavia, Turkey or Pakistan, but their countries of origin were not indicated clearly in the article. FRG, familial renal glucosuria.
these two mutations were not detected in 100 chromosomes derived from 50 healthy and unrelated individuals, or in the three SNP databases retrieved for this study, indicating that this is not a common polymorphism. Moreover, the pathogenicity prediction based on three online algorithms demonstrated that the mutations p.W172R and p.P514S may be deleterious. A previous in vitro functional expression study of SLC5A2 mutations demonstrated that six missense mutations (c.294C>A, c.736C>T, c.1051T>C, c.1400T>C, c.1420G>C and c.1691G>A) appeared to affect transport activity by reducing intrinsic transporter activity, impairing protein insertion into the cell membrane, suppressing protein synthesis and promoting protein removal or degradation (15). Therefore, it is thought that these two mutation sites may be of particular functional significance in the pathogenesis of FRG.

Further in vitro research projects on kidney cells involving the construction of specific plasmids are required to confirm the pathogenic nature of these mutations.

According to a review of the literature, 86 mutations in the SLC5A2 gene have been reported to be associated with FRG. Missense, frameshift and splicing mutations are the most common among these. It is likely that mutations of the SLC5A2 gene may occur among different demographic groups. Among the 115 patients with FRG considered in the present study, there is no specific age at diagnosis that is most common, nor a significant sex difference. A majority of severe FRG cases exhibit mutation states that are homo-zygous or compound heterozygous, suggesting that the mode of inheritance may be explained as a co-dominant pattern with incomplete penetrance. It is noteworthy that three FRG patients had no mutations in the SLC5A2 gene (4,9). In addition, not all individuals with similar or identical mutations have the same degree of increased glucose excretion, suggesting a role for non-genetic factors or other genes in glucose transport. Also, other SGLTs that are known to be expressed in the kidney and whose functions have not yet been clarified are candidate modified genes in cases of FRG (4,31).

In conclusion, the present study identified a compound heterozygous mutation (p.W172R and p.P514S) of the SLC5A2 gene in a Chinese patient with FRG. The mechanism whereby the p.W172R and p.P514S mutations impair SGLT2 function, in addition to the exact mechanism of abnormal glucose transport in FRG, requires further investigation.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
SL and ZY conceived and designed the experiments. SL conducted the experiments. YY, LH and MK were involved in conducting the experiments. SL collected the data and wrote the paper. ZY revised the manuscript. All authors read and approved the final paper.

Ethics approval and consent to participate
The study was approved by the Institutional Review Board of the Third Xiangya Hospital, Central South University.
(Changsha, China), and written informed consent was obtained from all participants.

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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