Genetic and clinical insights into acute kidney injury in maturity-onset diabetes of the young caused by the *ABCC8* c.2500C>T mutation: Potential risk factors associated with SGLT2 inhibitors

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Abstract. Mature-onset diabetes of the young (MODY) is an autosomal dominant genetic disease that is typically diagnosed during childhood or early adolescence. The primary pathogenesis of MODY involves gene mutations that impair insulin synthesis and/or secretion by islet β cells, rendering the condition independent of insulin resistance. A family with the MODY-12 phenotype caused by an ATP-binding cassette subfamily C member 8 (*ABCC8*) gene mutation was investigated in the present study. Clinical data were collected from all family members, and second-generation gene sequencing and Sanger sequencing were performed. The suspected pathogenic mutation was validated by Sanger sequencing, and the three-dimensional structure of the pathogenic variant protein was predicted and simulated using the Swiss-Model platform. Five individuals with MODY-12, including the proband, were identified in this family. Second-generation gene sequencing confirmed that all family members carried the *ABCC8* c.2500C>T (p.Arg834Cys) mutation. Structural modeling revealed that the replacement of arginine at position 834 in the wild-type protein with cysteine results in the formation of an additional hydrogen bond with the surrounding amino acids. In addition, the *ABCC8* c.2500C>T carriers in this family experienced recurrent diabetic ketoacidosis and acute kidney involvement (AKI) phenotypes, and all patients had a history of sodium-glucose transporter 2 inhibitor (SGLT2i) use. We hypothesize that AKI in these patients may be pseudo-AKI associated with the use of SGLT2is. However, the proband exhibited symptoms indicative of rapidly progressing diabetic nephropathy. This study demonstrates that clinicians managing patients with MODY should be aware of the risk of acute and serious complications, particularly as SGLT2i may induce pseudo-AKI, which could ultimately compromise patients' long-term renal prognosis.

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Introduction

Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes caused by autosomal dominant mutations in a single gene that impair pancreatic β-cell function. Mechanistically, MODY differs from type 2 diabetes mellitus (T2DM) in that it involves the impaired synthesis and secretion of insulin rather than insulin resistance. MODY accounts for 1-2% of all diabetes cases in Europe (1). However, in China, improvements in genetic screening and clinical diagnostics have increased the diagnostic rate of MODY to ~9% (2). MODY is currently classified into 14 genetic subtypes due to mutations in the following genes: Hepatocyte nuclear factor

4a (*HNF4A*), *HNF1A*, *HNF1B*, glucokinase (*GCK*), pancreatic and duodenal homeobox 1, neuronal differentiation 1, KLF transcription factor 11, carboxyl ester lipase, paired box 4, insulin, B lymphocyte kinase, ATP-binding cassette subfamily C member 8 (*ABCC8*), potassium inwardly rectifying channel subfamily J member 11 and adaptor protein phosphotyrosine interacting with PH domain and leucine zipper 1. Among the various subtypes, HNF1A-MODY, GCK-MODY, HNF4A-MODY and HNF1B-MODY are the most commonly diagnosed (3). In 2011, Fajans and Bell (4) formally described the onset of MODY as occurring during childhood or early adolescence, typically in patients aged 9-14 years, although it may present even earlier. Previous studies have estimated that MODY accounts for ~1-5% of all diabetes cases in Western countries, such as Europe, North America and Australia. However, in Asian populations, including China, owing to differences in screening intensity and genetic architecture, the true prevalence of MODY may fall below or exceed this interval (5,6). Over time, MODY can lead to chronic complications affecting the eyes, kidneys, nerves and blood vessels (6).

The diagnostic criteria for MODY, proposed by Tattersall and Fajans (7) in 1975, comprise: i) Onset of diabetes before age 25 years; ii) diabetes in at least three family members across successive generations, indicating autosomal dominant inheritance; iii) presentation as non-insulin-dependent diabetes mellitus (NIDDM); iv) absence of obesity; and v) no history of diabetic ketoacidosis (DKA). Despite these diagnostic definitions, MODY remains rare and is frequently misdiagnosed as T2DM (8).

The present study describes a MODY-12 pedigree carrying a heterozygous pathogenic variant in the *ABCC8* gene, segregating in an autosomal dominant pattern. The index patient is a 22-year-old woman with a body mass index within the normal range (18.5-24.9 kg/m^2). Contrary to the classical diagnostic criteria for MODY, the patient experienced three episodes DKA within 10 months of diagnosis, along with a transient but rapid decline in renal function. While most patients with MODY-12 are currently managed with sulfonylureas, emerging evidence suggests that sodium-glucose transporter 2 inhibitors (SGLT2is) can be used in combination with sulfonylureas as an alternative treatment approach for MODY (9).

Materials and methods

Research subjects. A pedigree was recruited from the Provincial Hospital Affiliated to Fuzhou University (Fuzhou, China) between January and December 2024, which comprises five males and seven females, including five affected individuals (I-2, II-2, II-5, III-2 and III-4) with onset ages ranging from 19 to 22 years, consistent with typical MODY phenotypes. A pedigree exhibiting the MODY-12 phenotype was investigated (Fig. 1A). Next-generation sequencing (NGS) and Sanger sequencing methods revealed heterozygous pathogenic *ABCC8* variants in five affected individuals (I-2, II-2, II-5, III-2 and III-4), while seven unaffected relatives (I-1, II-1, II-3, II-4, II-6, III-1 and III-3) lacked these variants.

Clinical phenotype investigation. Detailed clinical information and medical records were collected for all pedigree members. Subsequently, NGS was conducted on each participant to identify pathogenic variants. The study protocol was approved by the Ethics Committee of Fujian Provincial Hospital (Fuzhou, China). Written informed consent was obtained from all participants or their legally authorized representatives.

Extraction of genomic DNA. Peripheral blood (2 ml) was collected from each participant in an EDTA-coated tube. Genomic DNA was subsequently extracted from the blood using a MolPure® Magnetic Blood DNA Kit (Shanghai Yeasen Biotechnology Co., Ltd.).

Clinical and biochemical assessments. During three hospitalizations of the proband (III-4), blood and urine samples were obtained to perform routine biochemistry, urinalysis, and assessment of insulin autoantibodies. Other affected family members (I-2, II-2, II-5 and III-2) underwent follow-up visits, during which peripheral blood was collected for measurement of fasting plasma glucose, serum insulin, insulin autoantibodies, and standard biochemical analyses.

Comprehensive second-generation sequencing: Whole-exome, copy number variation (CNV) and full-length mitochondrial genome profiling. For whole-exome sequencing, the purity and concentration of the extracted genomic DNA was assessed using a NanoDrop spectrophotometer (Thermo Fisher Scientific, Inc.) and a Qubit 3.0 fluorometer (Thermo Fisher Scientific, Inc.). Sequencing libraries were then constructed using the NadPrep DNA Rapid Digestion Library Preparation Module (cat. no. 1002601; MGI Tech Co., Ltd.) according to the manufacturer's instructions. This process included restriction enzyme digestion, end repair and A-tailing, adapter ligation and amplification by PCR. The ligated fragments were size-selected for an insert of ~320 bp using 50 μl NadPrep® SP Beads (cat. no. 1002211; MGI Tech Co., Ltd.). The libraries were then pooled and whole-exome regions were enriched using the NEXome Core Panel [cat. no. 1001852; Nanodigmbio (Nanjing) Biotechnology Co., Ltd.] and the Hybrid Capture Reagent [cat. no. 1005102; Nanodigmbio (Nanjing) Biotechnology Co., Ltd.]. Finally, high-throughput sequencing (150 bp; PE150) was performed on a DNBSEQ-T7 sequencer (MGI Tech Co., Ltd.). Raw sequencing data were generated and assessed with FastQC v 0.12.0 (https://www.bioinformatics.babraham.ac.uk/projects/fastqc/), Burrows-Wheeler Aligner v 0.7.17 (https://bio-bwa.sourceforge.net/), SAMtools/SAMtools markdup v 1.17 (https://samtools.sourceforge.net/), Picard MarkDuplicates v 3.1.0 (https://broadinstitute.github.io/picard/), GATK v 3.8 (https://gatk.broadinstitute.org/hc/en-us) and Exomiser v 12.1.0 (https://www.sanger.ac.uk/tool/exomiser/) for quality control. Following the removal of low-quality reads and adapter sequences, the clean reads were aligned with the reference genome using Burrows-Wheeler Aligner, and the resulting alignments were sorted using SAMtools. PCR duplicates were marked and removed using Picard MarkDuplicates and SAMtools markdup. Finally, variants were called with the Genome Analysis Toolkit (GATK) following the GATK Best Practices workflow. The clinical features of the proband were encoded using standardized Human Phenotype Ontology (HPO)

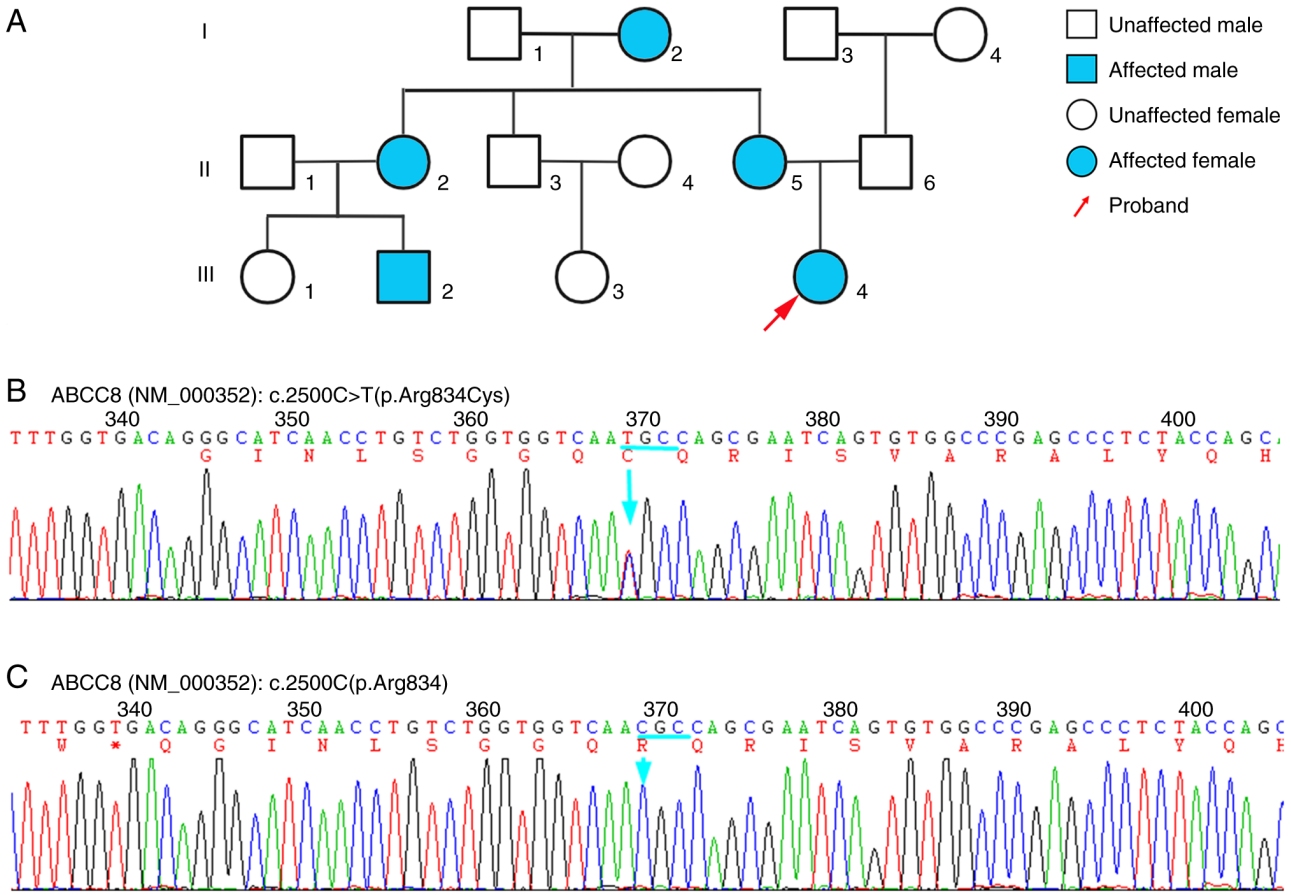

Figure 1. Pedigree and genetic analysis of a family affected by maturity-onset diabetes of the young-12. (A) Pedigree of the family. Squares denote males, circles denote females and blue shading indicates heterozygous carriers of the *ABCC8* c.2500C>T (p.Arg834Cys) variant. (B) Sanger sequencing chromatogram of the *ABCC8* gene, showing the location of the c.2500C>T (p.Arg834Cys) mutation in exon 21. (C) Sanger sequencing chromatogram of wild-type *ABCC8* exon 21, with the c.2500C nucleotide peak indicated by an arrow. ABCC8, ATP-binding cassette, subfamily C, member 8; C, cytosine; T, thymine; Arg, arginine; Cys, cysteine.

(https://hpo.jax.org/browse/search?q=MODY&navFilter=all). Variant prioritization and phenotype-driven ranking were performed using Exomiser by combining HPO annotations with the detected variants. Candidate variants were classified according to American College of Medical Genetics and Genomics (ACMG) guidelines, and pathogenicity was assigned based on established criteria (10). Allele frequencies were retrieved from the Genome Aggregation Database (gnomAD v 3.1.2; https://gnomad.broadinstitute.org/). Pathogenicity of missense variants was predicted using the Rare Exome Variant Ensemble Learner (REVEL); the functional impact of amino acid substitutions was assessed with Sorting Intolerant From Tolerant (SIFT); and the effects of missense variants or small insertions and deletions (indels) on protein structure and function were evaluated by the Polymorphism Phenotyping tool (PolyPhen).

A total of 56,705 candidate genes were initially considered. The following filters were then applied to exclude likely nonpathogenic variants. Variants with an allele frequency ≥1% in the ExAC (v0.3) (http://exac.broadinstitute.org/) or gnomAD (v 3.1.2) browsers were excluded. Variants with an allele frequency ≥5% in an in-house database (iGeneTechDB) were excluded. Synonymous variants outside of splice-site regions were removed. Variants classified as 'benign' or 'likely benign' in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar; updated March 2025) were excluded. After these steps, the remaining gene list was retained for downstream disease-association analysis. The c.2500C>T (p.Arg834Cys) variant in *ABCC8*

Table I. Examination indices of the proband during three hospital admissions.

	Admission			
Test item	First	Second	Third	Normal value
Biochemical indices				
Cr, μmol/l	1,187	1,220	2,236	44-133
UA, μmol/l	490	355	360	142-416
BUN, mmol/l	9.2	8.7	8.8	1.8-7.1
FBG, mmol/l	32.0	30.6	34.4	3.9-7.0
Urine tests				
Glucose	++++	++++	++++	-
Ketone	+++	++	++	-
Protein	+	+++	+++	-

Cr, creatinine; UA, uric acid; BUN, blood urea nitrogen; FBG, fasting blood glucose.

Table II. Clinical data of the family members with maturity-onset diabetes of the young.

Variable	Subject					Normal value
	III-4	III-2	II-2	II-5	I-2	
Onset age, years	22	19	20	20	21	-
BMI, kg/m^2	20.5	20.3	19.7	20.5	19.3	18.5-23.9
ABCC8 p.Arg834Cys	Yes	Yes	Yes	Yes	Yes	-
Polydipsia	Yes	Yes	Yes	Yes	Yes	-
Diuresis	Yes	Yes	Yes	Yes	Yes	-
Polyphagia	Yes	Yes	Yes	Yes	Yes	-
Obesity	No	No	No	No	No	-
AKI	Yes	Yes	Yes	Yes	Yes	-
DKA	Yes	Yes	Yes	Yes	Yes	-
Hyperlipidemia	Yes	Yes	Yes	No	Yes	-
Blurred vision	Yes	Yes	No	No	No	-
FPG, mmol/l	3.0	3.7	3.3	2.9	3.5	3.9-6.1
FINS, μIU/ml	24.6	23.2	25.1	24.8	26.2	5-20
HOMA-IR	3.3	3.8	3.7	3.2	4.1	≤1

BMI, body mass index; ABCC8, ATP-binding cassette, subfamily C, member 8; AKI, acute kidney injury; DKA, diabetic ketoacidosis; FPG, fasting plasma glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment-insulin resistance (FPG x FINS/22.5).

(NM_000352) was classified as likely pathogenic. To validate this finding, all available family members, with the exception of the proband, who underwent NGS, were screened by Sanger sequencing. Primers flanking the *ABCC8* c.2500C>T site were designed using Primer Premier 5.0 (Premier Biosoft International). Genomic DNA from the proband (III-4) and affected relatives (I-2, II-2, II-5 and III-2) was amplified by polymerase chain reaction using Taq DNA Polymerase (cat. no. D1806-250UN; Sigma-Aldrich Co., Ltd.) in 25-μl reactions. Thermal cycling was performed on a VeritiPro™ Thermal Cycler (cat. no. A48141; Thermo Fisher Scientific Co., Ltd.) with an initial denaturation at 95˚C for 5 min, followed by 35 cycles of 95˚C for 30 sec, annealing at 58˚C for 30 sec and extension at 72˚C for 45 sec, and a final extension at 72˚C for 7 min. The PCR products were purified and subjected to bidirectional Sanger sequencing on an ABI 3730XL Genetic Analyzer (Applied Biosystems; Thermo Fisher Scientific, Inc.). Sequencing chromatograms were analyzed with SeqMan Pro v14.1 (DNASTAR, Inc.), and genotype-phenotype cosegregation was evaluated across the pedigree. The primers used were as follows: Forward, 5'-GGAAGTGGCAGCACACATTC-3' and reverse, 5'-GCTCAGCCTGGGGTTGTATT-3'.

The NGS data were analyzed for CNVkit v 0.9.5 (https://cnvkit.readthedocs.io/en/stable/) using standard bioinformatics pipelines and mitochondrial DNA variants were screened against the MITOMAP (https://www.mitomap.org/MITOMAP) and ClinVar databases.

Bioinformatics analysis. The tertiary structure of the ABCC8 protein, also known as sulfonylurea receptor 1 (SUR1; UniProt ID: Q09428; https://www.uniprot.org/uniprotkb/Q09428) was predicted by homology modeling using SWISS-MODEL (https://swissmodel.expasy.org/repository/uniprot/Q09428) (11), with the *Rattus norvegicus* SUR1 cryo-EM structure (https://www.rcsb.org/structure/6BAA) as a template. Structural visualization and comparative analyses were conducted using University of California San Francisco (UCSF) ChimeraX v 1.7 software. Analyses included electrostatic surface potential mapping and the structural superimposition of wild-type and mutant (c.2500C>T) models. Deviations between the two structures in key regions, namely nucleotide-binding domain 2 (NBD2) and transmembrane helix 14, were quantified by root-mean-square deviation measurements. UCSF ChimeraX was implemented in Python 3.12.2 (http://www.python.org/). ChimeraX provides a modular framework comprising a core library providing fundamental functions, including atomic coordinate manipulation, molecular surface rendering and basic graphics operations, and plugin modules for performing advanced functionalities.

Results

Clinical phenotypes. The proband (III-4) was a 22-year-old woman initially diagnosed with T2DM. Subsequently, NGS led to the reclassification of her diagnosis as MODY-12 due to the detection of the heterozygous variant c.2500C>T (p.Arg834Cys) of *ABCC8*. Within 10 months of the MODY diagnosis, the patient experienced three episodes of DKA accompanied by acute kidney injury (AKI), occurring at 3, 7 and 10 months. The detailed clinical examination results of the proband are summarized in Table I. Each episode of DKA was characterized by fasting blood glucose levels >30 mmol/l, along with symptoms including nausea, vomiting, fatigue and loss of appetite. Following insulin therapy and fluid-electrolyte replacement, the patient's fasting blood glucose is maintained at <7.0 mmol/l and 2-h postprandial glucose remains <10.0 mmol/l (12). The patient's renal function normalized

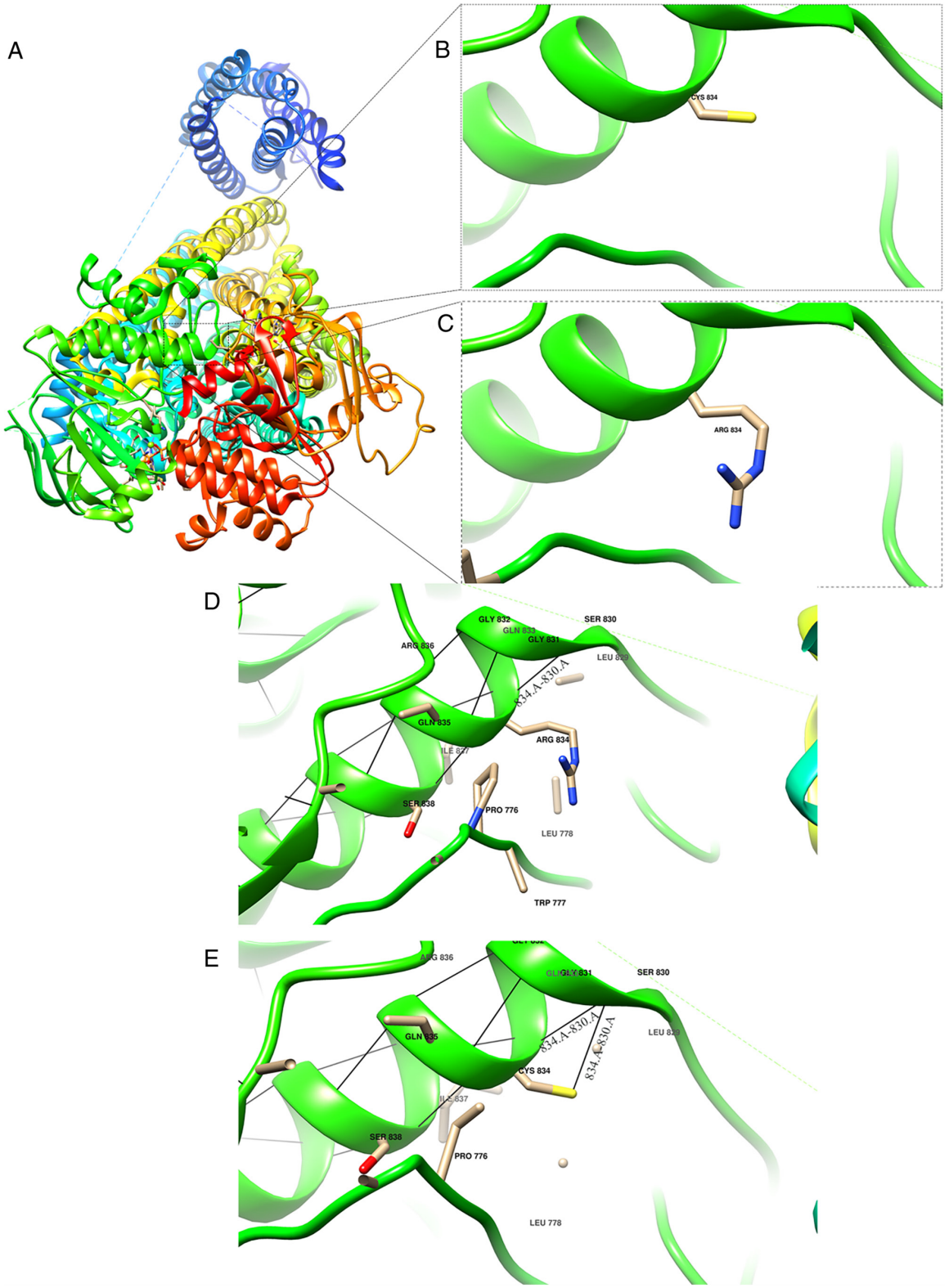

Figure 2. Modeling of the wild-type and p.Arg834Cys SUR1 proteins encoded by *ABCC8*. (A) Overall homology model of the *ABCC8*-encoded SUR1 protein. Detailed view of (B) the Arg834 side chain in the wild-type structure and (C) the Cys834 side chain in the p.Arg834Cys mutant. (D) Hydrogen-bonding interactions between Arg834 and adjacent residues in the wild-type model. (E) Altered hydrogen-bonding network of Cys834 with neighboring residues in the mutant model. ABCC8, ATP-binding cassette, subfamily C, member 8; SUR1, sulfonylurea receptor 1; Arg, arginine; Cys, cysteine.

rapidly after the first two AKI episodes, with serum creatinine returning to baseline within days. During the third DKA episode, the patient developed bilateral pedal edema, hyperlipidemia and hypertension, which were suggestive of nephrotic syndrome. However, renal ultrasound revealed no notable structural abnormalities.

In this MODY-12 pedigree, four other affected individuals (I-2, II-2, II-5 and III-2) were found to harbor heterozygous

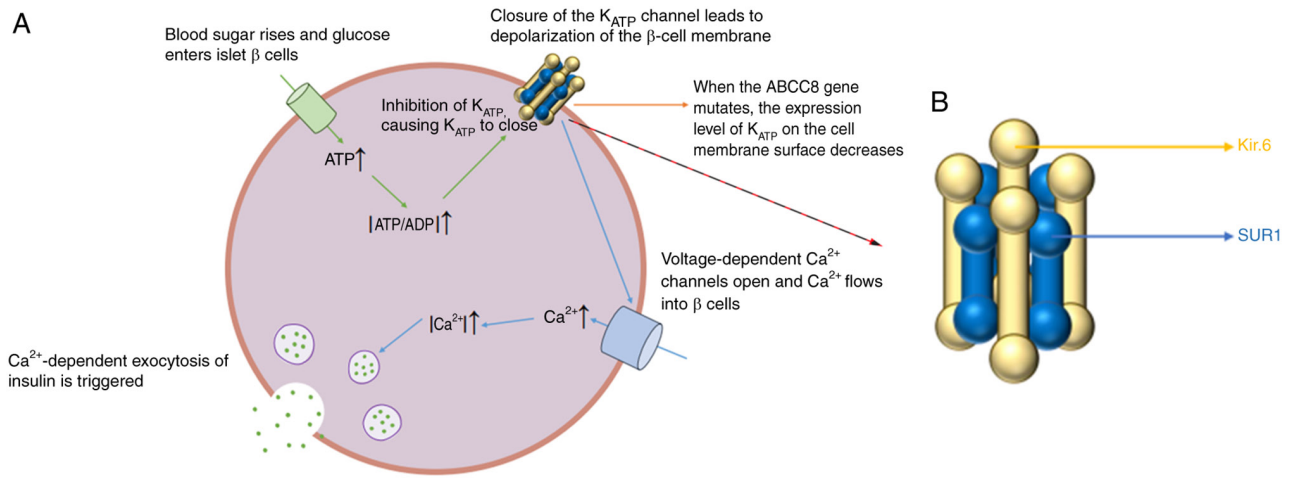

Figure 3. Function and structural organization of the K_{ATP} channel. (A) Role of the K_{ATP} channel in the secretion of insulin by pancreatic β cells. *ABCC8* c.2500C>T (p.Arg834Cys) mutation impairs K_{ATP} channel expression and activity, thereby disrupting membrane electrophysiology and reducing insulin secretion. (B) Schematic of the K_{ATP} channel octameric assembly, comprising four Kir6.2 pore-forming subunits and four SUR1 regulatory subunits. K_{ATP}, ATP-sensitive potassium; ABCC8, ATP-binding cassette, subfamily C, member 8; SUR1, sulfonylurea receptor 1; C, cytosine; T, thymine; Arg, arginine; Cys, cysteine.

pathogenic *ABCC8* variants. Notably, all carriers developed hyperglycemia before the age of 23 years and exhibited significantly reduced 2-h postprandial insulin secretion. These observations indicate that the *ABCC8* pathogenic variants impair pancreatic β-cell function, resulting in early-onset diabetes. Notably, the other affected family members also experienced DKA episodes accompanied by transient AKI (Table II). A review of medical histories revealed that all affected individuals had been treated with SGLT2is.

Comprehensive second-generation sequencing: Whole-exome, copy number variation and full-length mitochondrial genome profiling. The second-generation gene sequencing results revealed a heterozygous missense mutation in the *ABCC8* gene of the proband. This mutation involved the substitution of cytosine (C) with thymine (T) at base 2,500 in exon 21, which resulted in a change of the encoded amino acid at position 834 from arginine to cysteine, resulting in an altered protein tertiary structure (Fig. 1B and C). The *ABCC8* c.2500C>T mutation identified in the proband is registered in the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/variation/303772/). The mutation site has been reported by Japanese scholars (13). Although annotated as ambiguous/possibly benign by the Human Gene Mutation Database (HGMD), this mutation has been reported in patients diagnosed with NIDDM (10). The allele frequency of this gene mutation site in the East Asian population is 0.0003. It has a REVEL score of 0.852 (indicates a potential impact on protein function) and is predicted to be damaging or deleterious by SIFT and PROVEAN, respectively. According to ACMG guidelines, the combination of PS4_Supporting (indicates that the variant is observed at a significantly higher frequency in the patient cohort than in the control cohort), PP3 (indicates that multiple statistical methods predict the variant will exert a deleterious effect on the gene or its gene product) and PP1 criteria (denotes that the mutation co-segregates with the disease within the pedigree) indicates a likely pathogenicity. In summary, these findings indicate that the mutation at this site is pathogenic and deleterious. In the investigated family, the heterozygous carriers of this variant (III-4, III-2, II-5, II-2 and I-2) all presented with diabetes, whereas the remaining family members did not carry this variant or have a history of diabetes.

NGS data were analyzed for CNVs and mitochondrial DNA variants, but no phenotype-associated CNVs or pathogenic/likely pathogenic variants were detected.

Bioinformatics analysis. Homology models of the wild-type and p.Arg834Cys mutant proteins were generated using SWISS-MODEL (Fig. 2A). Structural superimposition revealed that the p.Arg834Cys substitution, where the positively charged arginine at residue 834 in the NBD2 region of SUR1 is replaced with neutral cysteine, induces local conformational alterations (Fig. 2B and C). In the wild-type structure, Arg834 forms a single hydrogen bond with Ser830, whereas in the p.Arg834Cys mutant, Cys834 forms two hydrogen bonds with Ser830 (Fig. 2D and E). These alterations induce conformational alterations that disrupt the native tertiary fold of the protein. Since protein function is associated with its tertiary structure, these perturbations are expected to impair SUR1 activity.

Discussion

Among all monogenic forms of diabetes, MODY is the most prevalent. However, despite the diversity of its subtypes, the overall occurrence of MODY in clinical practice remains relatively low, particularly for the rarer subtypes, including MODY-4 and MODY-6 to MODY-14 (1). The *ABCC8* gene is associated with MODY-12. As of April 2023, the HGMD had cataloged 737 distinct mutations in *ABCC8*, highlighting high genetic heterogeneity. Of these, missense and nonsense mutations are the most common, accounting for 502 cases. Other reported mutation types include splicing mutations (100 cases), small deletions (81 cases), small insertions (25 cases), gross deletions (16 cases), small indels (5 cases),

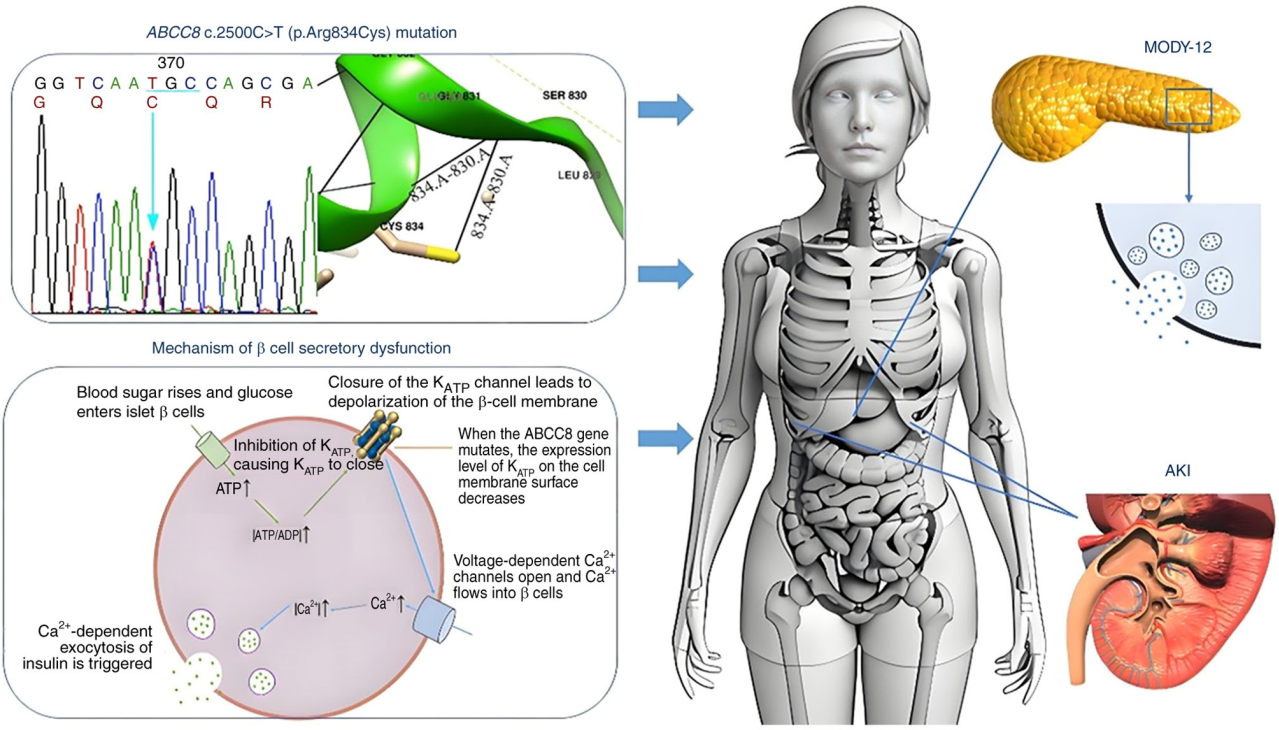

Figure 4. Graphical abstract illustrating the effects of the pathogenic *ABCC8* variant. The *ABCC8* c.2500C>T (p.Arg834Cys) pathogenic variant disrupts the tertiary structure of the protein and compromises K_{ATP} channel activity and glucose-stimulated insulin secretion in pancreatic β cells, thereby culminating in the clinical manifestations of MODY-12 and AKI. K_{ATP}, ATP-sensitive potassium; ABCC8, ATP-binding cassette, subfamily C, member 8; C, cytosine; T, thymine; Arg, arginine; Cys, cysteine; MODY-12, maturity-onset diabetes of the young-12; AKI, acute kidney injury.

gross insertions/duplications (5 cases), complex rearrangements (2 cases) and regulatory mutations (1 case).

In the present study, NGS and Sanger sequencing revealed that all affected individuals in the pedigree with MODY-12 harbored the *ABCC8* c.2500C>T (p.Arg834Cys) mutation. To assess the potential structural impact of this variant, the SWISS-MODEL server was employed to construct the three-dimensional structure of the mutant protein. This demonstrated that the genetic mutation results in the substitution of arginine at residue 834 with cysteine, which induces spatial conformational changes, primarily due to changes in local electrostatic interactions and steric effects. The most fundamental difference between the mutant and wild-type protein is in the properties of the amino acid side chains; the substitution of the positively charged, elongated side chain of Arg834 by the neutral, shorter side chain of Cys834 disrupts the local electrostatic potential and markedly diminishes steric hindrance. In addition, the hydrogen bonding network is critical for the structural integrity of the protein. However, following the mutation, an additional hydrogen bond is predicted to form between the residue at position 834 and Ser830, altering both the number and orientation of hydrogen bonds. This restricts the conformational flexibility of these residues and ultimately distorts the secondary structure of the 830-834 region. In addition, the reduction in steric hindrance may lead to an adaptive displacement of adjacent amino acid side chains, thereby compromising the stability of local hydrophobic residues. Furthermore, Cys834 has the potential to form disulfide bonds under oxidative conditions, which could promote aberrant dimerization (14). Disulfide bond formation may also interfere with the normal folding process of the SUR1 protein, as observed by 200-nsec molecular dynamics simulations and documented in K_{ATP} channelopathies (15). Collectively, these structural alterations are predicted to lead to a pronounced conformational rearrangement of the ATP-binding domain, disrupting key residue interactions essential for ATPase activity and compromising the regulatory function of the protein.

A comprehensive review of the LitVar database indicates that *ABCC8* mutations are associated with numerous disorders, including congenital hyperinsulinemia, neonatal diabetes and MODY-12 (16,17). For patients harboring these mutations, particularly those leading to SUR1 subunit dysfunction, clinical management with oral sulfonylureas has demonstrated short-term efficacy and safety, as evidenced by significant reductions in glycated hemoglobin levels within 3 months. However, careful monitoring and the individualized adjustment of sulfonylurea dosage is essential to optimize treatment outcomes (18). In addition, a review of the literature on *ABCC8* gene mutations reveals several molecular mechanisms underlying MODY, as summarized in Fig. 3A (19,20). Mutations in the *ABCC8* gene primarily impair the expression and function of the K_{ATP} channel, which is essential for the release of insulin by pancreatic β cells. The K_{ATP} channel is an octamer composed of four Kir6.x pore-forming units and four regulatory SUR1 subunits (Fig. 3B). *ABCC8* mutations markedly reduce the surface expression of SUR1, thereby decreasing the overall abundance of functional K_{ATP} channels and disrupting glucose-stimulated insulin secretion (21). Furthermore, *ABCC8* modulates multiple facets of K_{ATP} channel activity, including ATP and Mg^{2+} sensitivity, β-cell

membrane excitability and the function of voltage-dependent Ca^{2+} channels (22). Notably, certain *ABCC8* mutations have been shown to reduce the ATP sensitivity of K_{ATP} channels by ~4-fold. Consequently, even under hyperglycemic conditions with compensatory changes in β cells that maintain normal intracellular ATP levels and ATP/ADP ratios, the closure of K_{ATP} channels is delayed, ultimately delaying the triggering of insulin secretion. The electrical activity of pancreatic β cells is essential for insulin exocytosis (19). However, when K_{ATP} channel function is compromised, β cells fail to depolarize normally, likely due to diminished K^+ efflux. This prevents the proper opening of voltage-dependent Ca^{2+} channels and reduces intracellular Ca^{2+} concentrations, thereby impairing Ca^{2+}-dependent insulin exocytosis (23). These findings have been substantiated by quantitative experiments using patch-clamp and calcium imaging techniques. Furthermore, the K_{ATP} channel contains two nucleotide-binding sites, NBF1 and NBF2, on the SUR1 subunit. NBF1 lacks ATPase activity and functions independently of Mg^{2+}, whereas NBF2 exhibits ATPase activity and is highly dependent on Mg^{2+}, particularly in pancreatic β cells (22). Certain *ABCC8* gene mutations increase the Mg^{2+} dependence of NBF2, thereby enhancing overall potassium currents (20), impairing K_{ATP} channel inhibition and ultimately suppressing insulin secretion.

SGLT-2is are widely used to manage hyperglycemia in patients with diabetes. They primarily function by inhibiting glucose reabsorption in the proximal renal tubules, thereby increasing urinary glucose excretion. This induces osmotic diuresis, resulting in a notable loss of body fluids (24). In its 2018 consensus report, the American Diabetes Association and the European Association for the Study of Diabetes emphasized the clinical value of SGLT-2is, recommending their use, supported by high-level evidence, in patients with chronic kidney disease (CKD) and heart failure (25). A 2022 meta-analysis of cardiovascular and renal outcomes further demonstrated that SGLT-2is not only confer cardio-renal benefits but also effectively reduce mortality in patients with T2DM and diabetic kidney disease. However, the meta-analysis excluded patients with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2, a subgroup that may respond differently to treatment, thus limiting the generalizability of its findings (26).

The long-term renal protection provided by SGLT-2is is attributed not only to their beneficial effects on cardiovascular risk factors, such as the lowering of blood pressure and improvement of glycemic control, but also to direct renal mechanisms, including the reduction of intraglomerular pressure and anti-fibrotic effects. These combined actions have been associated with a slower decline in eGFR and reduced proteinuria in clinical studies (27). Investigation of the potential cardiorenal protective benefits of SGLT-2is in patients with heart disease has revealed that the osmotic diuresis induced by these agents may exacerbate a hyperosmolar state and increase the risk of urinary retention (28). Several mechanisms may account for the occurrence of AKI in patients treated with SGLT-2is. First, these agents induce osmotic diuresis, leading to dehydration and a subsequent reduction in blood volume (29). Second, increased delivery of sodium to the distal nephron activates tubuloglomerular feedback, resulting in afferent arteriolar constriction. Third, SGLT-2is may promote renal artery vasoconstriction, further compromising renal blood flow. These hemodynamic alterations can collectively lead to a gradual decline in eGFR (30). Furthermore, SGLT2is may exacerbate hypoxia in the renal medulla by reducing local oxygen availability and increasing metabolic demand. This hypoxic state stabilizes hypoxia-inducible factor (31), resulting in its upregulation, which in turn elevates plasma erythropoietin levels and promotes reticulocytosis (32).

Pseudo-AKI is a clinical phenomenon characterized by transient increases in serum creatinine or reductions in eGFR caused by extrarenal factors, rather than intrinsic damage to the renal parenchyma (33). Pseudo-AKI in patients with MODY-12 is particularly complex. In addition to the transient eGFR reductions induced by SGLT2i therapy, recurrent DKA episodes and various comorbidities act as critical triggers. Firstly, recurrent DKA can impair renal function through two main mechanisms: i) Severe dehydration and a reduction in effective circulating blood volume may lead to prerenal AKI (29) and ii) metabolic acidosis may trigger renal vasoconstriction, further decreasing renal perfusion and the eGFR (34). Additionally, CKD reduces the intrinsic resilience of the kidney to acute insults by inducing structural damage and impairing adaptive repair mechanisms, with reported odds ratios indicating a significantly increased risk. Furthermore, cardiovascular diseases, such as heart failure, reduce cardiac output below critical thresholds, thereby diminishing renal perfusion and imposing additional hemodynamic stress on the kidneys. The use of nephrotoxic agents further exacerbates renal impairment (35), for example, non-steroidal anti-inflammatory drugs inhibit cyclooxygenase-2, leading to a reduction in the production of prostaglandin E_2, which is essential for tubular repair (36). Similarly, contrast agents can trigger oxidative stress, as evidenced by increased malondialdehyde levels, thereby inducing cellular injury (37). Genetic factors also contribute to renal vulnerability. Specific mutations in the *ABCC8* gene, such as p.Arg834Cys, disrupt the function of K_{ATP} channels in β-cells, resulting in abnormal lipolysis and elevated free fatty acid levels. These metabolic disturbances can overwhelm the capacity of the kidney to adapt, further destabilizing renal function. In the present study, it was hypothesized that the pseudo-AKI observed in this pedigree may result from a synergistic interaction between pharmacological and genetic factors. Specifically, treatment with SGLT2is increases sodium excretion, potentially reducing the effective circulating volume and altering renal tubular dynamics, thereby mimicking AKI. Concurrently, the *ABCC8* c.2500C>T (p.Arg834Cys) mutation may impair K_{ATP} channel function, leading to metabolic disturbances that increase susceptibility to renal dysfunction. Together, these factors may contribute synergistically to the development of pseudo-AKI. A schematic summary of the study is presented in Fig. 4.

There are several limitations in the present study. First, the small sample size limits the ability to perform a comprehensive analysis of the heterogeneity of renal complications in MODY-12. To address this, a dedicated MODY-12 disease database is under development and multi-center cooperative studies with a larger cohort are planned, thereby increasing statistical power and improving the generalizability of the findings. Second, although the structure of the mutant *ABCC8*-encoded protein was preliminarily predicted using Swiss-Model, the impact of the mutation on the dynamic conformation of the protein was not thoroughly investigated.

In future studies, molecular dynamics simulation software, such as Gromacs, Sybyl or Discovery Studio, will be employed to simulate and analyze the wild-type and mutant proteins over an extended time scale. This approach will help to reveal mutation-induced conformational changes, alterations in the free energy landscape, and modifications in the interaction network of key residues. These future studies will provide deeper insights into the molecular mechanisms underlying the functional impact of the *ABCC8* mutation and lay a theoretical foundation for the development of precise treatment strategies.

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Availability of data and materials

The data generated in the present study may be found in the ClinVAR repository under accession number VCV000303772.9 or at the following URL: https://www.ncbi.nlm.nih.gov/clinvar/variation/303772/, and in the NCBI BioProject database under accession number PRJNA1251783 or at the following URL: https://dataview.ncbi.nlm.nih.gov/object/PRJNA1251783.

Authors' contributions

JZ, XC, HPY, YC, DDR, JZ and KYH acquired the data. QC, JHZ, LZ, MZG and YMG conducted the data analysis and interpretation. JXL, JZ, XC, LC and HPY wrote the manuscript. LC, JXL and TMW made critical revisions to the manuscript. JXL, TMW, LSL and JWL conceived and designed the study. JWL and JZ confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Fujian Provincial Hospital (Fuzhou, China; K2024-01-027), and all procedures were performed in accordance with the tenets of the Declaration of Helsinki. All participants and legal guardians of the minors involved in the present study provided written informed consent.

Patient consent for publication

Written informed consent for publication was obtained from the patients.

Competing interests

The authors declare that they have no competing interests.

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