Review Article

Clinical and Genetic Characteristics of ABCC8 Nonneonatal Diabetes Mellitus: A Systematic Review

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Objectives. Diabetes mellitus (DM) is a major chronic metabolic disease in the world, and the prevalence has been increasing rapidly in recent years. The channel of K$_{ATP}$ plays an important role in the regulation of insulin secretion. The variants in ABCC8 gene encoding the SUR1 subunit of K$_{ATP}$ could cause a variety of phenotypes, including neonatal diabetes mellitus (ABCC8-NDM) and ABCC8-induced nonneonatal diabetes mellitus (ABCC8-NNDM). Since the features of ABCC8-NNDM have not been elucidated, this study is aimed at concluding the genetic features and clinical characteristics.

Methods. We comprehensively reviewed the literature associated with ABCC8-NNDM in the following databases: MEDLINE, PubMed, and Web of Science to investigate the features of ABCC8-NNDM.

Results. Based on a comprehensive literature search, we found that 87 probands with ABCC8-NNDM carried 71 ABCC8 genetic variant alleles, 24% of whom carried inactivating variants, 24% carried activating variants, and the remaining 52% carried activating or inactivating variants. Nine of these variants were confirmed to be activating or inactivating through functional studies, while four variants (p.R370S, p.E1506K, p.R1418H, and p.R1420H) were confirmed to be inactivating. The phenotypes of ABCC8-NNDM were variable and could also present with early hyperinsulinemia followed by reduced insulin secretion, progressing to diabetes later. They had a relatively high risk of microvascular complications and low prevalence of nervous disease, which is different from ABCC8-NDM.

Conclusions. Genetic testing is essential for proper diagnosis and appropriate treatment for patients with ABCC8-NNDM. And further studies are required to determine the complex mechanism of the variants of ABCC8-NNDM.

1. Introduction

Diabetes mellitus (DM) is a major chronic metabolic disease in the world, and its prevalence has increased rapidly in recent years. Genetic and environmental conditions contribute to DM. The type of monogenic diabetes is the main etiology for diabetes. Maturity-onset diabetes of the young (MODY) is a kind of monogenic diabetes characterized by autosomal dominant inheritance. It is reported that the prevalence of MODY is 1 ~ 5% [1]. The activating variants of ABCC8 also could cause MODY. The ABCC8 gene encoding sulfonylurea receptor (SUR), which is the regulatory subunit of K$_{ATP}$ channel, plays a key role in regulating insulin secretion [2, 3]. K$_{ATP}$ channel is a hetero-octamer and consists of four inwardly rectifying proteins of the potassium channel Kir6.2 and four regulatory subunits of the sulfonylurea receptors [4, 5]. The enhanced glucose metabolism results in a change of ADP/ATP and leads to the closure of the K$_{ATP}$ channel, which in turn induces membrane depolarization and triggers the opening of the voltage-dependent Ca$^{2+}$ channel, which stimulates the release of insulin [6, 7]. Besides, variants in ABCC8 gene could cause hyperinsulinemic hypoglycemia (HH) due to inactivating variants which have an impaired response to magnesium adenosine diphosphate- (MgADP-) mediated opening of the channel [6, 8, 9]. Therefore, variants in ABCC8 gene could cause variable phenotypes: diabetes and HH, due to the different effects of the variants on channel function [9–13]. According to the onset age, DM induced by the ABCC8 variants are classified as two major groups of disorders—ABCC8-induced nonneonatal diabetes mellitus (ABCC8-NNDM) and ABCC8-induced neonatal diabetes.
mellitus ABCC8-NDM. Although the features of ABCC8-NDM have been well evaluated, the studies on the clinical and genetic features of ABCC8-NDM were limited. And these studies were mainly conducted in Europe and America. Bowman et al. first identified ABCC8 missense variants as a cause of MODY by testing sulfonylurea-sensitive HNF1A and HNF4A variant-negative MODY cases with no family history of neonatal diabetes [10]. Then, Johansson et al. identified a patient with ABCC8-MODY by exome sequencing in an analysis of variant-negative MODY cases by Sanger sequencing [14]. Additionally, potential pathogenic alterations in the ABCC8 gene were also identified in genetic studies. It has been shown that the prevalence of ABCC8 variants was estimated to be 0.5 ~ 1.5% in different cohorts [15–17]. However, the clinical phenotype has not been well established. In addition, the development in the field of ABCC8 gene-related diabetes has included de novo variants identified by new rapid molecular genetic features, symptoms, and medical therapy (sulfonylureas, DPP4-inhibitor).

Therefore, we systematically reviewed the literature related to ABCC8-NDM and ABCC8-NNDM to comprehensively conclude the genetic and clinical features of ABCC8-NDM. The review article has summarized the updated advance of ABCC8-NNDM and included de novo variants, clinical symptoms, and medical therapy.

### 2. Materials and Methods

**2.1. Study Subjects.** A total of 144 patients with ABCC8-NDM were included to analyze the clinical and genetic features in previous literature. The literature search has been conducted until Sep. 2020. We systematically identified all potentially relevant articles from the following electronic databases: MEDLINE, PubMed, and Web of Science. Search terms about diabetes—such as “maturity-onset diabete of the young (MODY),” “Neonatal diabetes mellitus,” “Neonatal diabetes” and “ABCC8-MODY,” and Sulfonylurea receptor 1, for example, “Sulfonylurea receptor 1,” “ABCC8,” and “KATP channels”—were used in various combinations and permutations across the databases. Language restriction (English) was applied. The criteria for inclusion were patients with ABCC8-NDM and those with ABCC8-NDM in previous studies. We systematically reviewed the related studies, including population-based studies, reviews, functional studies, and meta-analysis. The criteria for exclusion were repetitive literature and unavailable data. The genetic information of ABCC8 gene was as follows: accession number: NM_000352.4, NP_000343.2.

For data extraction, clinical information, including demographics, initial presentation, treatment of diabetes, physical examination results, laboratory test results, and information of genetic variants of the patients, was extracted.

**2.2. Classification of the Pathogenicity of ABCC8 Variants.** The pathogenicity of the variants was classified according to the established guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) [18]. We classified these variants into the following categories: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign. We used two or more lines of computational evidence (PROVEAN (http://provean.jcvi.org), SIFT (http://sift.jcvi.org/), Polyphen2 (http://genetics.bwh.harvard.edu/pph2/index.shtml), and MutationTaster (http://mutationtaster.org)) to support a deleterious effect on the gene for pathogenic supporting 3 (PP3) according to the guidelines of the ACMG-AMP. According to the guidelines, each pathogenic criterion is weighted as very strong (PSV1), strong (PS1-4), moderate (PM1–6), or supporting (PP1–5).

**2.3. Conservation of the Variants.** We conducted multiple sequence alignment (MSA) to align sequences of ABCC8 protein from a few vertebrate species by ClustalW server (https://www.genome.jp/tools-bin/clustalw) to interpret the conservation of these sequences. The result of MSA from ClustalW was plotted using ESPript (Easy Sequencing in Postscript 3.0, http://espript.ibcp.fr) [19, 20]. The species and GenBank accession numbers of the ABCC8 sequences adopted were the following: Homo sapiens—NP_000343.2, Callithrix jacchus—XP_035121815.1, Chlorocebus sabaeus—XP_008003585.1, Danio rerio—NP_001166118.2, Sus scrofa—XP_008003585.1, and Vulpes vulpes—XP_025863953.1. We followed the methods of Li et al. [21].

**2.4. Statistical Analysis.** Normally distributed variables were expressed as mean ± SD, and they were compared using t-tests. Categorical variables were presented as numbers and percentages. A Chi-square was adopted for categorical data. Analyses were performed using SPSS version 23.0.

### 3. Results

**3.1. The Clinical and Genetic Characteristics of Patients with ABCC8-NDM Described in Previous Studies.** We have systematically reviewed the literature reporting variants in ABCC8-NDM. Among the probands, 66 patients were reported as having ABCC8-NDM (including 139 patients with heterozygous variants, 21 patients with homozygous variants, one patient with a mosaic variant, and 14 patients with compound heterozygous variants) variants. All these patients were of different molecular mechanisms. Then, those variants led to impaired insulin secretion and diabetes, as shown in Table 1. Among those probands, 66 patients were reported as having transient neonatal diabetes mellitus, 92 as having permanent neonatal diabetes, and 17 as having an unknown type of diabetes due to a lack of follow-up. These variants caused ABCC8-NDM with either a dominant or recessive genetic pattern and were scattered throughout the functional regions of the gene (Table 1 and Supplementary Figure 1). All these patients presented with impaired insulin secretion, and 18 of the 110 variants were confirmed to be activating in functional studies and affect the channel inhibition by different molecular mechanisms. Then, those variants led to impaired insulin secretion and diabetes, as shown in Table 1.

The birth weight of 99 probands was available. Thirty-two probands (32%) had a birth weight < 2,500 g, and only one proband (1%) had a birth weight of >4,000 g. Forty-three of the 175 (24.6%) probands with ABCC8-NDM had
Table 1: Variants of ABCC8 causing neonatal diabetes mellitus reported in previous studies.

| Topological domain | Variant (protein effect)                                                                 | Zygosity   | Neurological features                   | Reference          |
|-------------------|-----------------------------------------------------------------------------------------|------------|----------------------------------------|--------------------|
| **TMD0**          | p.S8R, p.V86A, p.V86G, p.A90V, p.F132V, p.L135P, p.149F, p.F132L* p.N72S                | Het        | DEND                                   | [39, 50, 58, 64–66]|
|                   | p.E208K, p.D209E, p.D209N, p.Q211K, p.D212E, p.D212N, p.D212Y, p.R126C, p.L225P, p.T229N, p.R285Q, p.G296R | Het        | Muscle hypotonia                       | [58, 59, 70]       |
|                   | p.D212I                                                                                  | Het        | Hypotonia                              | [2, 50]            |
|                   | p.L213P, p.L213R*, p.R306H                                                               | Het        | DEND                                   | [40, 50, 59, 72, 73]|
|                   | p.A269D                                                                                  | Hom        | Slow ideation                         | [2, 23, 40, 59]    |
|                   | p.T229I                                                                                  | CH         | DEND                                   | [58, 59, 64]       |
|                   | p.E208K + p.Y263D                                                                         | Het        | DEND                                   | [2, 13, 50, 53, 59, 65, 73–78] |
| **TMD1**          | p.V324M, p.A355T, p.E350D, p.I395F, p.H410Y, p.S459R, p.Q485H, p.F536L, p.E577L, p.I585T | Het        | Seizure                                | [79]               |
|                   | p.D424V                                                                                  | Het        | DEND                                   | [40, 50, 59, 70, 81]|
|                   | p.C435R*, p.L451P, p.V587G                                                                | Het        | Hypotonia                              | [2, 50]            |
|                   | p.L582V*                                                                                 | Hom        | Slow ideation                         | [50, 59, 64, 69, 82]|
|                   | p.E382K, p.E382V                                                                         | Hom        | iDEND                                  | [2, 24, 50, 52, 54, 58, 59, 63, 68–70, 87] |
| **NBD1**          | p.V607M, p.R653Q, p.R825W, p.G382C, p.G832D, p.H862Y, p.R877Q, p.D979V, p.E939K         | Het        | iDEND                                  | [2, 4, 50, 52, 58, 59, 63, 68–70, 87] |
|                   | p.R825W*                                                                                 | Hom        | iDEND                                  | [2, 4, 50, 52, 54, 58, 59, 63, 68–70, 87] |
|                   | p.E747X, p.R825W                                                                         | Hom        | iDEND                                  | [2, 4, 50, 52, 54, 58, 59, 63, 68–70, 87] |
| **TMD2**          | p.H1023Y*, p.S1053N, p.F1176L, p.Q1178R*, p.R1182Q*, p.R1182W*, p.F1181S, p.P1198L*, p.G1255S | Het        | Seizure                                | [50, 60]           |
|                   | p.N1122D                                                                                 | Hom        | DEND                                   | [96]               |
|                   | p.H1023R*                                                                                | Hom        | DEND                                   | [97]               |
|                   | p.F1163L                                                                                 | Hom        | Muscle weakness and seizures          | [69, 82, 98]       |
|                   | p.A1184E                                                                                 | Hom        | DEND                                   | [50, 59, 64]       |
| **NBD2**          | p.R1313H, p.R1379S, p.I1424V*, p.E1506Q*, p.E1506D*, p.E1506G*, p.V1522M                | Het        | Hyperkinesia                           | [2, 13, 25, 26, 40, 50, 52, 58, 59, 66, 70, 73, 85, 89–95] |
|                   | p.R1379H                                                                                 | Het        | Minor dystonia                         | [23, 40, 50, 52, 59, 70, 76, 100] |
|                   | p.R1379C*                                                                                | Het        | DEND                                   | [50, 58, 59, 100]   |
|                   | p.R1379L*                                                                                | Het        | Motor delay                            | [101]              |
| **L0 + NBD1**     | p.V215I + p.V607M, p.L225P*, p.D879N                                                     | CH         | CH                                     | [58, 102, 103]     |
| **L0 + NBD2**     | p.T229I + p.V1522L                                                                       | CH         | CH                                     | [58, 59, 64]       |
| **L0 + TMD1**     | p.P207S + p.Y179X                                                                        | CH         | CH                                     | [59, 64]           |
| **NBD1 + TMD0**   | p.E747X + p.E128K                                                                        | CH         | CH                                     | [88]               |
neurological manifestations. In addition, 21 (12.0%) patients had developmental delay and epilepsy syndrome (DEND), 5 (2.9%) patients had intermediate DEND syndrome, 5 (2.9%) had developmental delay and epilepsy syndrome (DEND), 5 (2.9%) had other neurological symptoms. In addition, 21 (12.0%) patients had hyperinsulinemic hypoglycemia in early life and progressed to diabetes later.

In addition, twelve variants (including p.A269D, p.G296R, p.R306H, p.C435R, p.L582V, p.V607M, p.R825W, p.R1182W, p.R1182Q, p.P1198L, p.F1067I, and p.R1379H) of ABCC8 were reported both in patients with ABCC8-NDM and in those with ABCC8-NNDM (Table 2 and Figure 1). The above variants were located in the domains of the L0 linker region (L0), transmembrane domain 1 (TMD1), nucleotide-binding domain 1 (NBD1), transmembrane domain 2 (TMD2), and nucleotide-binding domain 2 (NBD2) (Figure 1). The same variant could cause different onset ages of diabetes.

### 3.2. The Genetic Characteristics of Patients with ABCC8-NDM Reported in Previous Studies

| Topological domain | Variant (protein effect) | Zygoty | Neurological features | Reference |
|--------------------|--------------------------|--------|-----------------------|-----------|
| NBD2 + TMD2        | p.E1327K+ p.V1523A + T1043QsX74 | CH     |                       | [59, 64, 104] |
| TMD0 + L0          | p.A30V* + p.G296R*         | CH     |                       | [105]     |
| TMD0 + NBD1        | p.N23H+ p.R825W            | CH     | Reduced consciousness, seizures | [58, 59, 64, 106] |
| TMD0 + NBD2        | p.P45L+ p.G1400R           | CH     |                       | [107]     |
|                    | p.L147R + p.R1379C         | CH     |                       |           |
| TMD0 + TMD2        | p.R168C+ p.G1256S          | CH     |                       | [108, 109] |
| TMD1 + TMD2        | p.V324M + p.R1394L         | CH     | DEND                  | [65]      |
|                    | p.L438F+ p.M1289V, p.I544T+| CH     |                       |           |
|                    | p.R1214W, p.N426S+ p.R1182Q| CH     |                       |           |
| TMD2 + L0          | A1263V + I196N             | CH     |                       | [52]      |

ATP-binding cassette transporter subfamily C member 8 (ABCC8) (accession number: NM_000352.4) has 17 transmembrane helices arranged in groups of five (N-terminal transmembrane domain (TMD0)), six (TMD1), and six (TMD2). Two large cytosolic loops follow TMD1 and TMD2 and contain the nucleotide-binding domains (NBDs, including NBD1 and NBD2) that are characteristic of ATP-binding cassette (ABC) proteins. The L0 linker region is located between the TMD0 and the TMD1 domains. ABCC8-NDM: ABCC8 variant-induced neonatal diabetes mellitus; Het: heterozygous; Hom: homozygous; CH: compound het; DEND: developmental delay and epilepsy syndrome; i-DEND: intermediate DEND syndrome. * indicates that the variant has been demonstrated to be activating in functional studies.

### 3.2.1. Evolutionary Conservation of Sites of Variants Both in Patients with ABCC8-NDM and in Those Patients with ABCC8-NNDM

The conservation analysis was carried out using ClustalW and ESPript 3.0 tools. Multiple sequence alignments of ABCC8 in the vertebrate species were selected for this analysis to show the sequence conservation of amino acid residues between them (Figure 2). It has been demonstrated that the amino acid residues of these twelve variants of ABCC8 both in ABCC8-NDM and ABCC8-NNDM in the literature were conserved across the organisms queried.

### 3.2.2. ABCC8-NDM due to Gain-of-Function and Loss-of-Function of Variants

Previous studies reported that both gain-of-function and loss-of-function variants in ABCC8 could cause diabetes. The first loss-of-function ABCC8 variant was a heterozygous inactivating ABCC8 p.E1506K variant, which presented with HH, followed by glucose intolerance and diabetes in later life [31]. This distinct phenotype...
Table 2: Variants of ABCC8 causing ABCC8-NNDM reported in previous studies.

| Topological domain | Variant (protein effect) | Zygosity | Neurological features | Reference |
|--------------------|--------------------------|----------|-----------------------|-----------|
| TMD0               | p.S53C, p.V84I, p.E100K  | Het      |                       | [10, 110, 111] |
|                    | p.L171F                  | Hom      |                       | [112]     |
| L0                 | p.P201S, p.A235T, p.A269D, p.G296R, p.R306C, p.R306H† | Het |                     | [15, 16, 32, 111, 113, 114] |
| TMD1               | p.A355T, p.Y356C*, p.R370S*, p.C418R, p.C435R*, p.Q485R, p.V563D, p.L582V*† | Het |                     | [10, 15, 23, 27, 111, 113, 115, 116] |
| NBD1               | p.V607M*, p.R620C, p.G658V, p.D673N, p.N780S, p.R825Q, p.R825W*, p.G832S, p.Q833K, p.H862R, p.E970V, p.A1536T | Het |                     | [15, 16, 37, 83, 87, 111, 113, 117–120] |
| TMD2               | p.G1008S, p.K1022Q, p.L1147R, p.R1182W*, p.R1182Q**, p.P1198L**, p.E1205K, p.N1244D, p.F1067I† | Het |                     | [10, 16, 111, 116, 118, 121] |
|                    |                          | Hom      |                       | [96]      |
| NBD2               | p.R1352H, p.A1366T, p.R1379H*, p.K1384Q, p.S1385F, p.A1390V, p.L1430F, p.Q1458E, p.A1472T, p.G1478R, p.R1493G, p.M1504T, p.E1506K*, p.A1507P, p.M1513T, p.V1523L, p.A1536V, p.R1538Q | Het |                     | [1, 10, 14–17, 31, 33, 37, 113, 115, 116, 118, 122–127] |
|                    | p.A1457T, p.R1418H*, p.R1420H* | Het | Epilepsy              | [36]      |
|                    |                          | Hom      |                       | [29, 30, 128] |
| TMD0               | p.H103Y + p.R74Q         | CH       |                       | [35]      |
| L0                 | p.G214R + p.V222M        | CH       |                       | [10]      |
| NBD1               | p.R933X + c.3992–9G > A, p.F793Sfs71 + c.4608+4A > G | CH |                     | [120, 129] |
| TMD2               | p.L1191L6X1207 + p.R1250X | CH       |                       | [129]     |
|                    | p.L1147R + p.R1250X      | CH       |                       | [129]     |
| NBD2               | p.R1420H + F5916604X     | CH       |                       | [128]     |

ABT-binding cassette transporter subfamily C member 8 (ABCC8) (accession number: NM_000352.4) has 17 transmembrane helices arranged in groups of five (N-terminal transmembrane domain (TMD0)), six (TMD1), and six (TMD2). Two large cytosolic loops follow TMD1 and TMD2 and contain the nucleotide-binding domains (NBDs, including NBD1 and NBD2) that are characteristic of ATP-binding cassette (ABC) proteins. The L0 linker region is located between the TMD0 and the TMD1 domains. “Neurological features” excludes seizures caused by hypoglycemia. ABCC8-NNDM: ABCC8 variant-induced nonneonatal diabetes mellitus; Het: heterozygous; Hom: homozygous; CH: compound het. * indicates that the damaging effect of the variant has been demonstrated in functional studies. # indicates that the variants have been reported to cause ABCC8-NDM and ABCC8-NNDM.

Figure 1: A schematic of the transmembrane topology of SUR1 showing the location of the variants both in ABCC8-NDM and ABCC8-NNDM. The transmembrane domains (TMD) include TMD0, TMD1, and TMD2. The nucleotide-binding domains (NBD) are indicated by NBD1 and NBD2, and the cytosolic linker L0 is between TMD0 and TMD1. ABCC8-NDM: ABCC8-induced neonatal diabetes mellitus; ABCC8-NNDM: ABCC8-induced nonneonatal diabetes mellitus.
was demonstrated in a mouse model carrying the p.E1506K variant of \textit{ABCC8} [28] and in patients carrying other rare variants of \textit{ABCC8}, such as p.R370S, p.R1418H, and p.R1420H [29, 30, 32]. Two Japanese probands with hypoglycemia in infancy due to heterozygous inactivating variants progressing to hyperglycemia were also reported [33, 34]. Therefore, the subtype of \textit{ABCC8}-NNDM due to inactivating variants could implicate the etiology of diabetes.

Among the 87 probands previously reported, 24% (21/87) carried inactivating \textit{ABCC8} variants reported in hyperinsulinemia, whereas 24% (21/87) carried activating \textit{ABCC8} variants were also associated with NDM. And the remaining 52% (45/87) carried variants with undetermined molecular mechanism. In the previously reported cases of \textit{ABCC8}-NNDM, it was estimated to be \~25% patients with activating \textit{ABCC8} variants and \~25% with inactivating variants. The molecular mechanisms of the remaining \~50% variants were needed further investigation.

3.2.3. The Clinical Characteristics of Patients with \textit{ABCC8}-NNDM Reported in Previous Studies. A total of 144 patients with \textit{ABCC8} variants including the probands and their hyperglycemic relatives (125 Caucasians, 15 East Asians, three Africans, and one Chinese) were analyzed. The clinical
and genetic characteristics of them are shown in Table 2 and Supplementary Table 1. The diagnosed age was reported in 71 probands. Among them, three (4%) were diagnosed with diabetes when <6 years old, 28 (39%) when 6–18 years old, and 40 (56%) when 18–40 years old. According to their body mass index (BMI) at diabetes onset, 10 (27%) of the 37 patients (seven probands and three relatives) who were diagnosed when ≥18 years old were overweight or obese. According to the available data, 30 patients were described using sulfonylureas (SUs) for glucose control. 22/30 (73.3%) patients have shown to be effective with SUs, while the levels of HbA1c were less than 7.0%. We found that just three probands with ABCC8 variants, including compound variants of p.H103Y and p.R74Q and missense variants of p.A1457T and p.E1506K, had microalbuminuria [35–37]. Reilly et al. have described that retinopathy was also common microvascular complication and that 5 out 10 patients with ABCC8 variants had diabetic retinopathy [37]. A similar case was reported by Ovsyannikova et al. [36], where the patient was diagnosed with diabetes at age 27 years (p.A1457T variant in ABCC8), and during the initial investigation, he had nonproliferative retinopathy and a raised microalbumin creatinine ratio.

As is known to all, neurological features are essential for ABCC8-NDM, and forty-three (24.6%) probands had neurological manifestations among the 175 reported probands with ABCC8-NDM according to the published literature. In the ABCC8-NDM group, just one proband with the variant of p.A1457T had epilepsy independent of hypoglycemia [36], and two probands with the variants of p.R1418H and p.R1420H had seizure due to hypoglycemia [29, 30]. Compared with the ABCC8-NDM group, the frequency of the neurological phenotype in the ABCC8-NDM group was significantly lower (1/87 (1%) vs. 43/175 (24.6%), P < 0.001), and we did not include neurological features due to hypoglycemia.

We have described above that there were 24 probands carrying activating variants, 24% carried inactivating variants, and 52% carrying undetermined variants among the 87 probands. Based on the available data, we further compared the clinical features between the probands with activating and inactivating variants. There was no significant difference in diagnosed age and BMI between the two groups (diagnosed age: 28.9 ± 11.6, n = 14 vs. 19.1 ± 10.0, n = 0.981, P = 0.960; diagnosed BMI: 22.5 ± 3.3, n = 6 vs. 22.5 ± 4.3, n = 9, P = 0.981). Among the inactivating variants, two probands with the variants of p.R1418H and p.R1420H had seizures due to hypoglycemia [29, 30], while no probands were reported with neurological symptoms among the activating group. And one proband with inactivating p.E1506K variant had microalbuminuria [37]. In addition, the prevalence of hyperinsulinemia and hypoglycemia was significantly higher in the inactivating group than the activating group (13/21 (61.9%) vs. 0/21 (0.0%), P < 0.001).

4. Discussion

To the best of our knowledge, it is the first time for our study to systematically review the literature and comprehensively investigate the genetic and clinical features of ABCC8-NDM. From the previous studies, we identified 144 patients with ABCC8-NDM and found that ~25% and ~25% of the previously reported ABCC8-NDM cases had activating and inactivating ABCC8 variants, while the remaining ~50% had uncertain functional variants. These patients had relatively successful glucose control after the treatment of SUs and might have a relative high risk of diabetic microvascular complications.

As is known to all, gain-of-function variants in the ABCC8 gene are one of the main causes of NDM. With the development of genetic analysis, the ABCC8 variants in NNDM were also reported. Many potential pathogenic alterations were also identified in ABCC8. A study performed in a French adult type 2 diabetic outpatient cohort with 139 patients identified two (1.5%) likely causative variants in ABCC8 [15]. Another study in a large cohort of nonobese patients with diagnosed age <40 years and a family history of diabetes found 8 (8/1564, 0.5%) ABCC8 variants [16]. In addition, an East Asian study found one (0.9%) ABCC8 variant among 109 suspected monogenic diabetes patients [17]. The prevalence of ABCC8 variants was estimated to be 0.5–1.5% in different studies. It suggests that the subunit K\textsubscript{ATP} channel of SUR1 encoding the ABCC8 gene is responsible for a small subset of NNDM.

The ABCC8 gene encodes SUR subunit of K\textsubscript{ATP} channels, which links cell metabolism to electrical activity by regulating potassium movement across the membrane [38]. Closure of the channel as a result of ATP-binding led to β-cell membrane depolarization and opening of voltage-dependent and calcium-channels and calcium mediated release of insulin. Activating variants in the ABCC8 gene led to an increased probability of opening of the potassium channel, therefore preventing any activation of the voltage-dependent calcium channel and any glucose-induced insulin secretion [39], leading to NDM, early onset diabetes, and MODY [10, 40]. In previous studies, there are 18 variants that were confirmed to be activating by functional studies. However, the pathophysiology of inactivating variants in ABCC8 means that lack of functional K\textsubscript{ATP} channels leads to depolarized β-cells and elevation of cytosolic calcium, which result in continuous insulin secretion and independent of plasma glucose concentration [6, 8]. In addition, 21 (24%) probands with dominant loss-of-function variants in ABCC8 previously reported could cause hyperinsulinism in the early period and progress to diabetes later. Four inactivating variants (p.R370S, p.E1506K, p.R1418H, and p.R1420H) have been demonstrated to decrease K\textsubscript{ATP} channel activity and dysregulation of insulin secretion in functional studies, with the consequence that patients with these variants progressed to diabetes in later life. As a consequence, both activating and dominantly inactivating variants have been considered the key cause of ABCC8-NDM.

The underlying mechanism by which loss-of-function variants of ABCC8 subsequently cause the remission of HH and future hyperglycemia is complex and required to be elucidated. Recently, basal insulin secretion was observed to be elevated in human islets with inactivating ABCC8 variants, but insulin secretion response to glucose was impaired.
And apoptotic beta cells increased in transgenic mice with inactivating K\textsubscript{ATP} channels [42, 43]. Besides, insulin content and gene expression decreased and led to the disruption of insulin secretion and glucose intolerance in the mouse model with an inactivating variant of ABCC8 [28]. The above factors could partly address the mechanism by which K\textsubscript{ATP} defects cause diabetes in patients with loss-of-function variants. To date, there have been far-from adequate functional studies to elucidate the exact impact of different variants. Further studies are still needed to account for the complex underlying mechanisms resulting in the remarkable phenotypic heterogeneity related to inactivating ABCC8 variants.

Great importance is to be attached to the diabetic complications. It could be seen that just three probands with variants were reported to have diabetic kidney injury. It is uncertain whether patients with ABCC8-NNDM had a higher risk of diabetic kidney disease (DKD). Mice with the homozygous ABCC8 p.E1506K\textsuperscript{+/-} variant (an inactivating variant), presenting with hyperinsulinemia early in life followed by diabetes and early DKD later in life, were observed [28, 44]. In the mouse model, glucose could induce histone modifications, which drove the expression of proinflammatory genes and thereby predisposed to diabetic kidney disease. Further studies are also required to confirm the risk and the precise diabetic kidney disease mechanism of ABCC8 variants. Besides, the frequency of diabetic retinopathy was ~50 percent among the patients with ABCC8 variants. Although dyslipidaemia, hypertension, and possible genetic factors contribute to the early manifestation of diabetes complications, the ABCC8 variants may be responsible for the rapid progression to proliferative retinopathy. SUR1 is also expressed in the retinal vessels, and glibenclamide could inhibit adenosine-induced retinal vasodilation [45, 46], which occurs by interacting with K\textsubscript{ATP} channels in retinal vessel pericytes. In models of postinfarct central nervous system oedema, the SUR1 expression has been observed to upregulate in injured nervous tissue, and inhibiting SUR1-induced ion channel modulation with the drug glibenclamide could protect the central nervous system from ischaemia-reperfusion and traumatic brain injury [47].

As we known, neurological features are important features for ABCC8-NDM. From the published literature, we found that sixty (34%) probands had neurological manifestations among 175 reported probands with ABCC8-NDM. K\textsubscript{ATP} channels are predominately expressed in endocrine tissues such as the pancreatic islet cells and the nervous system. The deleterious effect on the nervous system of K\textsubscript{ATP} channel activating variants is likely related to the neurological features, including more severe DEND and iDEND [48, 49]. The reported variants associated with a neurological phenotype were distributed across all functional regions of the gene, while only one patient had a neurological manifestation independent of hypoglycemia (1%) among patients with ABCC8-NNDM [36]. Compared to the ABCC8-NDM group, the frequency of a neurological phenotype in the ABCC8-NNDM group was significantly lower. Activating variants reduce the ability of ATP to inhibit ion channel activity, thus increasing the magnitude of the K\textsubscript{ATP} current, which hyperpolarizes brain and muscle cells and accounts for the neurological phenotype [39, 50, 51].

According to the previous published studies reporting SUs on the treatment of ABCC8 variants induced diabetes, we found that 73.3% of the patients owing to ABCC8 variants with SUs got successful glucose control. As the widely used drugs for the treatment of type 2 diabetes, SUs could bind specifically to the SUR1 subunit, then closing the K\textsubscript{ATP} channel via an ATP-independent mechanism and therefore increasing the insulin secretion of β cells [52]. Several studies observed that patients with NDM were transferred to SUs successfully after molecular genetic diagnosis of ABCC8 variants [53, 54]. Up to 90–95% of patients with NDM due to using ABCC8 and KCNJ11 variants are able to be taken off of insulin therapy after initiation of SUs therapy [55, 56]. A recent meta-analysis also showed the estimated success rate was 90.1% in the SU treatment for ABCC8-NNDM [57]. Therefore, SUs are effective for diabetic patients due to activating ABCC8 variants. However, due to different types of variants and variable clinical phenotypes, the correct treatment may be different. In addition, the sensitivity to SUs was variable in patients with ABCC8 variants. As majority, but not all, patients were successful to transfer from insulin to SUs [58]. In addition, two Japanese patients with hypoglycemia in infancy progressed to diabetes later in life due to the ABCC8 heterozygous inactivating variants and got better glucose control treated with DPP4 inhibitors [33, 34]. It might be useful for patients with inactivating variants to be treated with incretin-related drugs. We need to consider the genetic features and the response of treatment to facilitate individualized therapy. Although we systematically reviewed the previous studies on ABCC8-NNDM, the sample size was limited. More studies are needed to better summarize its characteristics. In addition, we found that a few patients in the case reports were effective for new hypoglycemic drugs, but there was a lack of randomized controlled trials and longitudinal follow-up studies to help us determine the long-term efficacy and the impact on complications and neuropathy. Although we used the ACMG guideline to interpret the pathogenicity of ABCC8 variants, the precise molecule mechanisms are still needed to clarify in vivo and vitro studies.

5. Conclusion

Our study comprehensively concluded the genetic and clinical features of ABCC8-NNDM. The variants of ABCC8-NNDM consist of activating and inactivating ones. The phenotypes of these patients varied with good effect for SUs and had a risk of diabetic complications. It is also essential to make a precise genetic diagnosis for appropriate treatment of them to reduce episodes of hypoglycemia and diabetic complications. Next generation sequencing (NGS) enables a rapid and cost-effective diagnosis, and it should be taken into consideration for the ABCC8 gene in early onset diabetes. In the future, studies are needed to account for the mechanisms resulting in the remarkable phenotypic heterogeneity related to ABCC8 variants.
Data Availability
The data used to support the findings of this study were included within the article.

Conflicts of Interest
We have no conflicts of interest to declare.

Authors’ Contributions
Meng Li conducted this study, analyzed the data, and completed the original manuscript. Linong Ji contributed to the study design, critically revised the manuscript, and obtained funding. Xueyao Han contributed to the study design and critically revised the manuscript. All authors read the final manuscript and approved the final submission. Linong Ji and Xueyao Han contributed equally to this work.

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Supplementary Materials
Supplement Table 1: the clinical and molecular genetic characteristics of the patients with ABCC8-NDM in the previous studies. Supplement Figure 1: a diagram illustrates the inheritance of ABCC8 variants in probands with neonatal diabetes mellitus and nonneonatal diabetes mellitus. Variants showed in red represent that the variants were identified both in neonatal diabetes mellitus and nonneonatal diabetes mellitus. Abbreviations: ABCC8-NDM: ABCC8 variant-induced neonatal diabetes mellitus; ABCC8-NNDM: ABCC8 variant-induced nonneonatal diabetes mellitus. STROBE statement—checklist of items that should be included in reports of cohort studies. (Supplementary Materials)

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