**KCNJ11, ABCC8 and TCF7L2 polymorphisms and the response to sulfonylurea treatment in patients with type 2 diabetes: a bioinformatics assessment**

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**Abstract**

**Background:** Type 2 diabetes (T2D) is a worldwide epidemic with considerable health and economic consequences. Sulfonylureas are widely used drugs for the treatment of patients with T2D. KCNJ11 and ABCC8 encode the K\(_{\text{ir6.2}}\) (pore-forming subunit) and SUR1 (regulatory subunit that binds to sulfonylurea) of pancreatic \(\beta\) cell K\(_{\text{ATP}}\) channel respectively with a critical role in insulin secretion and glucose homeostasis. TCF7L2 encodes a transcription factor expressed in pancreatic \(\beta\) cells that regulates insulin production and processing. Because mutations of these genes could affect insulin secretion stimulated by sulfonylureas, the aim of this study is to assess associations between molecular variants of KCNJ11, ABCC8 and TCF7L2 genes and response to sulfonylurea treatment and to predict their potential functional effects.

**Methods:** Based on a comprehensive literature search, we found 13 pharmacogenetic studies showing that single nucleotide polymorphisms (SNPs) located in KCNJ11: rs5219 (E23K), ABCC8: rs757110 (A1369S), rs1799854 (intron 15, exon 16 -3C/T), rs1799859 (R1273R), and TCF7L2: rs7903146 (intron 4) were significantly associated with responses to sulfonylureas. For *in silico* bioinformatics analysis, SIFT, PolyPhen-2, PANTHER, MutPred, and SNPs3D were applied for functional predictions of 36 coding (KCNJ11: 10, ABCC8: 24, and TCF7L2: 2; all are missense), and HaploReg v4.1, RegulomeDB, and Ensembl's VEP were used to predict functions of 7 non-coding (KCNJ11: 1, ABCC8: 1, and TCF7L2: 5) SNPs, respectively.

**Results:** Based on various *in silico* tools, 8 KCNJ11 missense SNPs, 23 ABCC8 missense SNPs, and 2 TCF7L2 missense SNPs could affect protein functions. Of them, previous studies showed that mutant alleles of 4 KCNJ11 missense SNPs and 5 ABCC8 missense SNPs can be successfully rescued by sulfonylurea treatments. Further, 3 TCF7L2 non-coding SNPs (rs7903146, rs11196205 and rs12255372), can change motif(s) based on HaploReg v4.1 and are predicted as risk factors by Ensembl's VEP.

**Conclusions:** Our study indicates that a personalized medicine approach by tailoring sulfonylurea therapy of T2D patients according to their genotypes of KCNJ11, ABCC8, and TCF7L2 could attain an optimal treatment efficacy.

**Keywords:** Sulfonylurea, Type 2 diabetes, Pharmacogenetics, ABCC8, KCNJ11, TCF7L2, Single nucleotide polymorphism, Bioinformatics, *In silico*
Background
The prevalence of diabetes is increasing at a fast rate, which was 6.4% (285 million) among adults aged 20–79 years in 2010, and will increase to 7.7% (438 million) by 2030 [1]. Among all diabetic cases, approximately 90% are patients with type 2 diabetes (T2D), which is associated with a number of microvascular complications including retinopathy, nephropathy, neuropathy, as well as macrovascular complications [2]. T2D is caused by a plethora of lifestyle and genetic factors [3, 4]. Current therapies for T2D include life-style modifications and use of oral antidiabetic drugs, with sulfonylurea being one of the most frequently used one [5]. There are a number of different sulfonylurea treatments for T2D patients, among which the commonly used ones are gliclazide, glibenclamide, glimepiride and glipizide [6].

Sulfonylurea promotes insulin secretion from the pancreatic β cells of the pancreas in a glucose-independent manner by binding to ATP-sensitive K⁺ (K\textsubscript{ATP}) channel on the cell membrane of pancreatic β cells. K\textsubscript{ATP} channel is a heterooctamer comprising the inward-rectifier potassium ion channels K\textsubscript{ir}6.x (i.e., K\textsubscript{ir}6.1 and K\textsubscript{ir}6.2) that form the pore, and sulfonylurea receptors (SUR; i.e., SUR1, SUR2A, and SUR2B) that regulate the opening and closing of its associated K\textsubscript{ir}6.x potassium channel, as SUR is sensitive to ATP and ADP levels. The binding of sulfonylureas to the corresponding receptors could lead to an efflux of intracellular potassium, hyperpolarization of the β cell membrane, and the opening of voltage-gated calcium channels, which result in an increased secretion of insulin to circulation (Fig. 1).

The pancreatic β cell K\textsubscript{ATP} channel consists of four pore-forming subunits of the inward-rectifying potassium channel K\textsubscript{ir}6.2 and four regulatory subunits of the SUR1 [7–9]. When blood glucose concentrations rise, an increase in glucose metabolism results in a change of ADP/ATP ratio, which leads to a closing of K\textsubscript{ATP} channel. The respective genes encoding K\textsubscript{ir}6.2 and SUR1, i.e., KCNJ11 and ABCC8, are located next to each other on human chromosome 11p15.15. Mutations in KCNJ11 or ABCC8 genes could decrease or abolish the metabolic sensitivity of β cell K\textsubscript{ATP} channel function, leading to a constant depolarization of the cell membrane and a persistent insulin secretion even at very low plasma glucose concentrations [10]. E.g., single nucleotide polymorphism (SNP) E23K (i.e., rs5219) of KCNJ11 gene is associated with T2D risk (reviewed in [11]), is shown to result in a decrease or loss of sensitivity of K\textsubscript{ATP} channel to the inhibitory effect of ATP [12] and/or an enhancement of activation by free fatty acids [13]. Further, mutations in ABCC8 gene could cause hyperinsulinemic hypoglycemia [10]. The β cell K\textsubscript{ATP} channel can be pharmacologically regulated by sulfonylureas, which function by binding to and closing the K\textsubscript{ATP} channel [14] that leads to membrane depolarization, which subsequently results in an activation of voltage-dependent calcium channels causing an influx of calcium, which then triggers insulin granule exocytosis.

**TCF7L2** encodes a member of the T-cell factor (TCF) transcription factor that plays a critical role in Wnt signaling pathway [15], which is shown to be involved in β cell dysfunction in T2D [16]. TCF7L2 is a member of the TCF-lymphocyte enhancer factor (LEF) protein family [17], and the bipartite transcription factor β-catenin/TCF-LEF serves as an effector of cAMP-dependent protein kinase A (PKA) signaling to mediate the physiological effects of peptide hormones including glucagon-like peptide-1 (GLP-1), which utilizes cAMP as a second messenger [18, 19]. TCF7L2 gene SNPs are strongly associated with a higher risk of T2D development [15], which could be mediated by their influences on blood glucose homeostasis [20].

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**Fig. 1** A schematic representation of the pancreatic β cell illustrating the molecular model for insulin secretion mediated by K\textsubscript{ATP} channel comprising KCNJ11 and ABCC8 subunits in sulfonylurea treatment
Sulfonylureas show considerable inter-individual variations in the hypoglycemic response, with approximately 10–20% of patients having a less than 20 mg/dl reduction in fasting plasma glucose (FPG) following the initiation of sulfonylurea therapy (called primary sulfonylurea failure) [21]. Further, about 50–60% of patients will initially have a greater than 30 mg/dl reduction in FPG, but will fail to reach the desired glycemic treatment goals [21]. In contrast, some T2D patients could have higher risks of mild or severe hypoglycemia in response to sulfonylurea treatment [22–24]. Molecular variants of sulfonylurea drug target genes KCNJ11, ABCC8, and TCF7L2 could lead to different responses to sulfonylurea therapy in T2D patients. Therefore, their impacts need to be carefully evaluated. The primary objective of this study is to predict functional effects of 36 coding (KCNJ11: 10, ABCC8: 24, and TCF7L2: 2) and 7 non-coding (KCNJ11: 1, ABCC8: 1, and TCF7L2: 5) SNPs that were identified from published literatures and MutDB database (http://www.mutdb.org/) by applying a spectrum of in silico bioinformatics tools. Each Kir6.2 subunit has two transmembrane domains called M1 and M2, and the pore-forming domain is located between them [25]. The locations of 10 missense SNPs (including the well-studied E23K) in the KCNJ11 protein that comprises 390 amino acids [26] are shown in Fig. 2, respectively. Each SUR1 subunit has three transmembrane domains, i.e., TMD0, TMD1, and TMD3, and two nucleotide binding domains, i.e., NBD1 and NBD2. Between TMD0 and TMD1, there is a cytosolic loop called CL3 [27]. The locations of 24 missense SNPs (including the well-studied A1369S) in the ABCC8 protein that comprises 1581 amino acids [28] are shown in Fig. 3. The human TCF7L2 gene consists of 17 exons, five of which are alternatively spliced (i.e., exons 4, 13, 14, 15, and 16) and exhibits tissue-specific expression [29]. The differential splicing of TCF7L2 potentially gives rise to three groups of protein isoforms (i.e., short-, medium-, and large-length isoforms) with highly differential functional properties. These three groups depend on the predicted stop codon usages, which are located in exons 15, 16, 17 [30]. To date, TCF7L2 intronic SNP, rs7903146, represents the most significant risk variant for T2D [31]. However, four other non-coding SNPs, i.e., rs7901695, rs7895340, rs11196205 and rs12255372, have also been significantly associated with an increased risk of T2D [32] and have been widely studied. The locations of these 5 non-coding SNPs in the gene structure of TCF7L2 (including the well-studied intronic SNP rs7903146) are illustrated in Fig. 4.

Methods

Literature search strategy

Comprehensive electronic literature searches of databases including PubMed, Google Scholar, Cochrane Library, Excerpta Medica Database (EMBASE) were performed up to June 1, 2016 using the following keywords: sulfonylurea, type 2 diabetes, KCNJ11, ABCC8, and TCF7L2. A manual search of the references cited in initially identified articles was also performed. Furthermore, we searched all relevant references of three comprehensive review articles [5, 33, 34]. The search was restricted to English language articles.

Inclusion and exclusion criteria

Randomized controlled trials and observational studies were eligible for inclusion in the current study. In vitro studies, animal studies, letters, reviews, and unrelated articles and duplicates were excluded from this study.

Data extraction

From each included study, the following data were extracted: first author, publication year, SNP name, gene name, National Center for Biotechnology Information (NCBI) dbSNP (http://www.ncbi.nlm.nih.gov/snp/) ID, study design, study subjects, control source, length of follow-up, and results.

In silico bioinformatics analysis

Computational predictions of functional impacts of non-synonymous SNPs (nsSNPs)

Five in silico tools were applied: (i) SIFT[35] (http://sift.jcvi.org/), (ii) PolyPhen-2 [36] (http://genetics.bwh.harvard.edu/
Computational predictions of functional impacts of non-coding SNPs

Three in silico tools were applied: (i) HaploReg v4.1 [40, 41] (http://www.broadinstitute.org/mammals/haploreg/haploreg.php), (ii) RegulomeDB [42] (http://regulomedb.org/), and (iii) Ensembl's VEP [43] (http://www.ensembl.org/Homo_sapiens/Tools/VEP?db=core).

Results

A total of 17 articles corresponding to 17 independent studies were qualified and subsequently included for evaluating the relationships between KCNJ11, ABCC8 and TCF7L2 SNPs and response to sulfonylurea in patients with T2D. The detailed characteristics of these 17 studies [44–60] were presented in Table 1. Of them, 13 studies
| Study ID | Author | Year | Gene Symbol | SNP Name | dbSNP ID | Study Design | Study Subjects | Control Source | Length of Follow-up | Results | Association |
|----------|--------|------|-------------|----------|----------|--------------|----------------|----------------|-------------------|---------|-------------|
| Study 1  | Gloyn et al. [44] | 2001 | KCNJ11 | E23K | rs5219 | RCT | 363 Caucasian T2D and 307 normoglycemic control subjects | UKPDS | 1 year | Variant allele did not significantly affect the response to SU therapy significantly | No |
| Study 2  | Sesti et al. [45] | 2006 | KCNJ11 | E23K | rs5219 | RCT | 525 Caucasian T2D patients with secondary SU failure | Hospital-based | NA | Secondary SU failure, K allele vs E allele (OR = 1.45; 95% CI 1.01–2.09; P = 0.04). Adjustment for age, gender, fasting glycemia, glycosylated hemoglobin, age at diagnosis, and duration of diabetes in a logistic regression analysis did not change this association (OR = 1.69; 95% CI: 1.02–2.78; P = 0.04) | Yes |
| Study 3  | Feng et al. [46] | 2008 | KCNJ11 | E23K | rs5219 | RCT | 1268 Chinese T2D patients treated with 8-week gliclazide | Hospital-based | 8 weeks | E23K variant of the KCNJ11 gene was significantly associated with decreases in FPG (P = 0.002). | Yes |
| Study 4  | Holstein et al. [47] | 2009 | KCNJ11 | E23K | rs5219 | Case–control | 43 T2D patients treated with gliclazide or glibenclamide | Hospital-based | NA | E23K variant was significantly associated with increased HbA1c levels (adjusted P = 0.004) independent of age, sex, body mass index, diabetes duration and SU dose. | Yes |
| Study 5  | Nikolac et al. [48] | 2009 | KCNJ11 | E23K | rs5219 | Cross-sectional | 228 Caucasian T2D patients with SU therapy | Hospital-based | NA | For KCNJ11 E23K polymorphism, for different genotype groups, there were no significant differences of FPG, PPG, and HbA1c concentrations (P = 0.143, 0.675, and 0.824, respectively). | No |
| Study 6  | El-sisi et al. [49] | 2011 | KCNJ11 | E23K | rs5219 | Case–control | 50 Egyptian T2D patients with secondary SU failure | Hospital-based | NA | Secondary SU failure, EK + KK vs. EE (RR = 1.65; 95% CI: 1.04–2.6; P = 0.04). | Yes |
| Study 7  | Javorsky et al. [50] | 2012 | KCNJ11 | E23K | rs5219 | RCT | 55 T2D patients with 6-month treatment of gliclazide | Hospital-based | 6 months | For ΔHbA1c EK + KK vs. EE (11.5 ± 0.09 vs. 8.0 ± 0.13, P = 0.036) | Yes |
| Study 7  | Javorsky et al. [50] | 2012 | KCNJ11 | E23K | rs5219 | RCT | 28 T2D patients with 6-month treatment of gliclazide | Hospital-based | 6 months | For ΔHbA1c EK + KK vs. EE (11.0 ± 0.12 vs. 0.0 ± 0.19, P = 0.0676) | No |
| Study 7  | Javorsky et al. [50] | 2012 | KCNJ11 | E23K | rs5219 | RCT | 14 T2D patients with 6-month treatment of glibenclamide | Hospital-based | 6 months | For ΔHbA1c EK + KK vs. EE (10.5 ± 0.11 vs. 0.98 ± 0.09, P = 0.633) | No |
| Study 8  | Ragia et al. [51] | 2012 | KCNJ11 | E23K | rs5219 | Case–control | 92 T2D patients (80 gliclazide/12 glibenclamide) who had experienced at least one drug-associated hypoglycemic event, while 84 T2D patients (74 gliclazide/10 glibenclamide) who had never experienced a hypoglycemic event | Hospital-based | NA | KCNJ11 E23K genotype and allele frequencies were not different between hypoglycemic and non-hypoglycemic T2D patients (P = 0.35 and 0.47, respectively). In logistic regression models before and after adjustment for other risk factors (age, body mass index, sulfonylurea mean daily dose, duration of T2D, renal function | No |
Table 1 Characteristics of included studies (N=17) (Continued)

| Study | Authors | Year | Gene | SNP | Study Type | Population | Location | Duration | Additional Information |
|-------|---------|------|------|-----|------------|------------|----------|----------|------------------------|
| 9     | Li et al. [52] | 2014 | KCNJ11 | E23K | RCT | 108 Chinese T2D patients treated with gliclazide for 16 weeks | Hospital-based | 16 weeks | Patients with the KK genotype had larger augmentations in changes (Δ) in acute insulin response (P=0.0049) and D body mass index (P=0.003); Patients with the EK genotype had a lower variance in changes in fasting insulin levels (P=0.049) and homeostasis model assessment of β cell function (P=0.0021) than those with the KK genotype |
| 9     | Li et al. [52] | 2014 | KCNJ11 | rs5219 | RCT | 108 Chinese T2D patients treated with gliclazide for 16 weeks | Hospital-based | 16 weeks | Yes |
| 10    | Glocyn et al. [44] | 2001 | KCNJ11 | L270V | RCT | 363 Caucasian T2D patients | UKPDS | 1 year | Variant allele did not significantly affect the response to SU therapy significantly |
| 10    | Meirhaeghe et al. [53] | 2001 | ABCC8 | Intron 15, exon 16 -3C/T | Cross-sectional | 70 T2D patients with SU therapy | 3 large representative French samples (in Lille, Strasbourg, and Toulouse) participating in the risk factor surveys of the WHO-MONICA | NA | For T2D patients treated with SU agents, those subjects bearing at least one -3C allele and had fasting plasma TG concentrations 35% lower than TT homozygotes [2.20 mmol/L (1.14–4.14) for TT vs. 1.43 mmol/L (0.81–2.52) for TC + CC; P = 0.026] |
| 11    | Zychma et al. [54] | 2002 | ABCC8 | Intron 15, exon 16 -3C/T | Case-control | 68 Caucasian T2D patients who required insulin treatment and had known diabetes duration 5 years, compared to 99 Caucasian T2D patients receiving SU alone or in combination with metformin or acarbose with known diabetes duration ≥15 years | Hospital-based | NA | There was no significant impact of ABCC8 exon 16 -3C/T polymorphism on the early ineffectiveness of SU treatment (P=0.04126 based on a Chi-square test) |
| 5     | Nikolac et al. [48] | 2009 | ABCC8 | Intron 15, exon 16 -3C/T | Cross-sectional | 228 Caucasian T2D patients with SU therapy | Hospital-based | NA | Yes |
| 12    | Nikolac et al. [55] | 2012 | ABCC8 | Intron 15, exon 16 -3C/T | Cross-sectional | 251 Caucasian T2D patients with SU therapy | Hospital-based | NA | Polymorphic allele carriers of the ABCC8 intron 15 -3C/T (which is 3 bp ahead of exon 16) polymorphism were more frequent in the subgroup of patients with the TG concentration increase after 6 months (P for genotype and allelic differences: 0.024 and 0.015, respectively) |

and CYP2C9 genotype, KCNJ11 E23K polymorphism did not affect hypoglycemia risk
| Study  | Authors          | Year | Gene          | SNP          | Study Design | Patients | Duration | Results |
|--------|------------------|------|---------------|--------------|--------------|----------|----------|---------|
| 13     | Zhang et al. [56] | 2007 | ABCC8         | A1369S rs757110 | RCT         | 115 T2D patients with gliclazide treatment for 8 weeks | Hospital-based | 8 weeks | For ΔHbA1c TG + GG vs. TT (1.60 ± 1.39 vs. 0.76 ± 1.70, P = 0.044) Yes |
| 3      | Feng et al. [46]  | 2008 | ABCC8         | A1369S rs757110 | RCT         | 1268 Chinese T2D patients treated with 8-week gliclazide | Hospital-based | 8 weeks | Compared with TT genotype, subjects with the GG genotype had a 7.7% greater decrease in FPG (P < 0.001), an 11.9% greater decrease in 2-h plasma glucose (P = 0.003), and a 3.5% greater decrease in HbA1c (P = 0.06) Yes |
| 14     | Sato et al. [57]  | 2010 | ABCC8         | A1369S rs757110 | Case–control | 32 patients with T2D admitted to hospital with severe hypoglycemia and 125 consecutive T2D outpatients without severe hypoglycemia, and all of the patients were taking glimepiride or glibenclamide | Hospital-based | NA | There were no significant differences in ABCC8 A1369S genotype distribution between patients with or without severe hypoglycemia (P = 0.26). Moreover, the A1369 allele tended to be less frequent in the hypoglycemic group (31 vs. 43%; OR = 1.65; 95% CI: 0.92–2.96; P = 0.09) No |
| 5      | Nikolac et al. [48] | 2009 | ABCC8         | R1273R rs1799859 | Cross-sectional | 228 Caucasian T2D patients with SU therapy | Hospital-based | NA | GG genotype of the ABCC8 exon 31 polymorphism had significantly higher HbA1c concentration compared to the AA genotype [7.8 (6.9–8.8) mmol/L vs. 6.3 (5.7–6.8) mmol/L; P < 0.001] Yes |
| 12     | Nikolac et al. [55] | 2012 | ABCC8         | R1273R rs1799859 | Cross-sectional | 251 Caucasian T2D patients with SU therapy | Hospital-based | NA | Wile-type G allele carriers had a significantly higher TG concentration when compared with the carriers of two variant A alleles (P = 0.023) Yes |
| 15     | Pearson et al. [58] | 2007 | TCF7L2        | NA rs7903146   | RCT         | 901 T2D patients with SU treatment | GoDARTS | 12 months | Carriers of the risk allele were less likely to respond to SUs with an OR for failure of 1.95 (95% CI: 1.23–3.06; P = 0.005), comparing rs12255372 TT vs. GG. Including the baseline HbA1c strengthened this association (OR = 2.16, 95% CI: 1.21–3.86; P = 0.009) Yes |
| 16     | Schroner et al. [59] | 2011 | TCF7L2        | NA rs7903146   | RCT         | 87 T2D patients with 6-month SU treatment in addition to metformin | Hospital-based | 6 months | Reduction in HbA1c CC vs. CT + TT is 1.16 ± 0.07 vs. 0.86 ± 0.07%, P = 0.003; Reduction in FPG: 1.37 ± 0.12 vs. 1.14 ± 0.14 mmol/L, P = 0.031) Yes |
| Study | Holstein et al. [60] | 2011 | TCF7L2 | NA | rs7903146 | RCT | 189 T2D patients with 6-month SU treatment | Hospital-based | 6 months | T allele was significantly more frequent in the group of patients who failed to respond to SU (i.e., those with HbA1c ≥ 7%) (36%) than in the control (i.e., those with HbA1c < 7%) group (26%) (OR = 1.57, 95% CI: 1.01-2.45, P = 0.046) | Yes |

*Studies are grouped by different genes. For each gene, studies are first sorted by SNP Name, then by Year, and then by Author, in ascending orders. Abbreviations: CI confidence interval, FPG fasting plasma glucose, Go-DARTS Genetics of Diabetes Audit and Research Study in Tayside Scotland, HbA1c glycosylated hemoglobin A1c, OR odds ratio, RCT randomized clinical trial, SNP single nucleotide polymorphism, SU sulfonylurea, SUR sulfonylurea receptor, T2D type 2 diabetes, TG triglyceride, UKPDS United Kingdom Prospective Diabetes Study, WHO-MONICA World Health Organization-Multinational MONItoring of trends and determinants of Cardiovascular diseases, NA not available.

**Because R1273R is a synonymous SNP, it is not included in functional prediction**
The most widely studied genetic polymorphism of *KCNJ11* for sulfonylurea response is E23K (i.e., rs5219) located in exon 1 [33]. However, functional effects of *KCNJ11* E23K polymorphism on the secretion and sensitivity of insulin in humans remain contentious [5]. Recent larger studies demonstrated that a significant reduction of insulin secretion, lower levels of insulin, and an improvement of insulin sensitivity were related to E23K variant in *KCNJ11* gene [61]. Moreover, E23K variant was associated with T2D development, which means that the K allele carriers had an increased risk of T2D [44, 62, 63]. Furthermore, some studies also found that the K allele carriers had better therapeutic response to gliclazide in comparison with the EE homozygous wild-type group [50], as well as an increased risk of sulfonylurea treatment failure [45, 49]. In addition, E23K variant was significantly associated with an increase of glycated hemoglobin A1c (HbA1c) level [47] and fasting glucose level that patients with the KK homozygous variant genotype had lower fasting glucose levels than those with the EE/EK heterozygous genotype [52]. Importantly, recent evidence demonstrated that patients with *KCNJ11* variants responded more efficiently to sulfonylurea than insulin [64–66]. Another *KCNJ11* polymorphism that was associated with sulfonylurea treatment responses is rs5210 which is located in 3'-untranslated region (UTR). A study conducted in two independent cohorts of Chinese T2D patients (cohort 1: n = 661, cohort 2: n = 607) treated with gliclazide demonstrated that *KCNJ11* rs5210 was positively associated with gliclazide response in cohort 1 study [46].

**ABCC8**

The most widely studied genetic polymorphism of *ABCC8* for sulfonylurea response is S1369A (i.e., rs757110) located in exon 33 [67]. This genetic variant was demonstrated to influence antidiabetic efficacy of sulfonylurea treatment in Chinese [46, 56], as well as an increased sensitivity to gliclazide [56]. More importantly, *KCNJ11* E23K and *ABCC8* S1369A, two common K<sub>ATP</sub> channel mutations that were in strong linkage disequilibrium, form a haplotype that appears to be associated with an increased T2D risk [68]. Additional *ABCC8* gene polymorphisms including rs1799854 (intron 15, exon 16 -3C/T) and rs1799859 (exon 31) had been shown to be associated with sulfonylurea treatment efficacy in Caucasians [48, 55].

**TCF7L2**

Previous studies have shown that several non-coding genetic variants of *TCF7L2* are associated with T2D risk in populations of diverse ancestries from countries encompassing United Kingdom [69], the Netherlands [70], Finland [32], Sweden [71], France [72], United States [73], India [74], and Japan [75] populations. Among these T2D-associated *TCF7L2* variants, rs7903146 (intron 4) showed the strongest association with T2D [76]. Significant reductions in HbA1c and fasting plasma glucose levels following a combined sulfonylurea and metformin treatment between T2D patients with CC genotype and those with CT/TT genotype were associated with *TCF7L2* rs7903146 variant allele [59]. Moreover, the rs12255372 variant, together with the rs7903146 variant, was shown to be associated with a significantly more frequent treatment failure [58–60]. It shall be noted that although in previous literatures, e.g., as in [32, 77], *TCF7L2* rs7901695 and rs7903146 are indicated to be in intron 3, and rs7895340,
rs11196205 and rs12255372 are indicated to be in intron 4, this is because exon 4, which is a variable exon, is often named as “3a” [78]. Because of a high incorporation in pancreatic β cells [79], exon 4 shall be included in the gene structure, such that rs7901695 and rs7903146 shall be indicated as located in intron 4, and rs7895340, rs11196205, and rs12255372 in intron 5, respectively, e.g., as in [80]. For the linear ordering of these 5 non-coding SNPs, according to the most updated (i.e., as of April 18, 2017) NCBI dbSNP, the chromosomal coordinates for rs7901695, rs7903146, rs7895340, rs11196205 and rs12255372 are 112994329, 112998590, 113041766, 113047288, and 113049143, respectively, on human chromosome 10 based on GRCh38.p7 assembly. Therefore, the linear ordering shall be rs7901695-rs7903146-rs7895340-rs11196205-rs12255372, as shown in Fig. 4 (all drawings in Figs. 1, 2, 3, and 4 are not to their exact scales and are for illustration purposes), which is agreement with that of [77].

**In silico bioinformatics analysis results**

For **KCNJ11**, **ABCC8** and **TCF7L2** genes, functional prediction results for 36 nsSNPs by SIFT, PolyPhen-2, PANTHER, MutPred, and SNPs3D were presented in Table 2, and those prediction results for 7 non-coding SNPs by HaploReg v4.1, RegulomeDB and Ensembl's VEP were presented in Table 3.

**Analysis of functional effects of nsSNPs by SIFT**

SIFT was used to predict the functional impact of an nsSNP on a protein molecule. An nsSNP with a SIFT score ≤ 0.05 is considered as having a deleterious effect on protein function [81]. A total of 22 nsSNPs were predicted to affect protein structure (SIFT score range: 0.00-0.05) including 4 **KCNJ11** missense SNPs (R192H, R201H, E227K, S385C), 16 **ABCC8** missense SNPs (G7R, N24K, F27S, R74W, E128K, V187D, R495Q, E501K, L503P, F686S, L1349Q, S1386F, L1389P, G716V, K1336N, L1349Q, S1386F, L1389P, D1471H) and 2 **TCF7L2** missense SNPs (P179H, K323N), whereas the remaining 14 missense SNPs were predicted to be tolerated (SIFT score range: 0.12–1.00) (Table 2).

**Analysis of functional effects of nsSNPs by PolyPhen-2**

PolyPhen-2 calculates a naïve Bayes posterior probability for a given mutation that it will be benign (PolyPhen-2 score < 0.15), possibly damaging (PolyPhen-2 score is greater than or equal to 0.15 but is less than 0.85), or probably damaging (PolyPhen-2 score ≥ 0.85), respectively [82]. A total of 25 nsSNPs were predicted to be probably damaging to protein function (PolyPhen-2 score range: 0.877–1.000), which includes 5 **KCNJ11** missense SNPs (V59M, I182V, R192H, R201H, E227K), 18 **ABCC8** missense SNPs (G7R, N24K, F27S, R74W, A116P, E128K, F132L, R495Q, E501K, L503P, F686S, G716V, L1349Q, S1386F, L1389P, R1420C, D1471H), and 2 **TCF7L2** missense SNPs (P179H, K323N), and the remaining 11 SNPs were classified as benign (PolyPhen-2 score range: 0.000–0.402) (Table 2).

**Analysis of functional effects of nsSNPs by PANTHER**

PANTHER characterizes likely functional effect of amino acid variation by means of a hidden Markov model-based statistical modeling and evolutionary relationship. The SNP with subSPEC score ≤ −3 is considered as intolerant or deleterious, whereas SNP with subSPEC score > −3 is classified to be less deleterious [83]. A total of 14 amino acid substitutions were classified as intolerant (subSPEC score range: from −8.97977 to −3.12006) including 3 **KCNJ11** missense SNPs (R27H, R192H, E227K), 9 **ABCC8** missense SNPs (L213R, R495Q, L503P, F686S, G716V, L1349Q, S1386F, L1389P, D1471H) and 2 **TCF7L2** missense SNPs (P179H, K323N), another 10 amino acid substitutions were classified as tolerated (subSPEC score range: from −0.69172 to 0.402), and the remaining 12 amino acid substitutions did not have subSPEC scores (Table 2).

**Analysis of functional effects of nsSNPs by MutPred**

MutPred predicts molecular causes of disease or deleterious amino acid substitution. A total of 30 nsSNPs had p-values > 0.5, which were considered to be functional [84] (MutPred P deleterious range: 0.566-0.981), which included 6 **KCNJ11** missense SNPs (V59M, I182V, R192H, R201H, E227K, L270V), 23 **ABCC8** missense SNPs (G7R, N24K, F27S, N72S, R74W, A116P, E128K, F132L, V187D, L213R, E382K, R495Q, E501K, L503P, F686S, G716V, K1336N, L1349Q, S1386F, L1389P, R1420C, I1424V, D1471H) and 2 **TCF7L2** missense SNPs (P179H, K323N) (Table 2).

**Analysis of functional consequences of nsSNPs by SNPs3D**

SNPs3D assigns molecular functional effects of nsSNPs based on structure and sequence analysis. Of the 36 nsSNPs, SNPs3D SVM score was available for only 7 nsSNPs (**KCNJ11**: 2, **ABCC8**: 3, and **TCF7L2**: 2). Of them, two nsSNPs, i.e., R1420C amino acid substitution of **ABCC8** gene and K323N amino acid substitution of **TCF7L2** gene, had SVM scores < 0, which were classified as deleterious substitutions [85] (Table 2).
| SNP ID | Gene Symbol | SNP Name | dbSNP ID | SNP Location | Chromosome Location (GRCh38.p7) | SIFT Score/Prediction | PolyPhen-2 Score/Prediction | PANTHER | PANTHER P_{deleterious} | MutPred | MutPred P_{deleterious} | SNPs3D Score |
|--------|-------------|----------|----------|--------------|---------------------------------|----------------------|--------------------------|----------|--------------------------|---------|-------------------------|-------------|
| SNP1   | KCNJ11      | E23K     | rs5219   | Exon 1       | 11:17388025                     | 1.00/Tolerated       | 0.001/Benign             | −0.69172 | 0.90044                  | 0.35     | 2                       |             |
| SNP2   | KCNJ11      | R27H     | NA       | Exon 1       | NA                              | 0.18/Tolerated       | 0.006/Benign             | −3.75303 | 0.67984                  | 0.248    | NA                      |             |
| SNP3   | KCNJ11      | V59M     | NA       | Exon 1       | NA                              | 0.12/Tolerated       | 0.999/Probably damaging | −2.72126 | 0.43076                  | 0.855    | NA                      |             |
| SNP4   | KCNJ11      | I182V    | NA       | Exon 1       | NA                              | 0.98/Tolerated       | 0.998/Probably damaging | −1.62168 | 0.20128                  | 0.684    | NA                      |             |
| SNP5   | KCNJ11      | R192H    | NA       | Exon 1       | NA                              | 0.01/Affect Protein Function | 1.000/Probably damaging | −6.9765  | 0.98159                  | 0.816    | NA                      |             |
| SNP6   | KCNJ11      | R201H    | rs80356624 | Exon 1     | 11:17387490                     | 0.00/Affect Protein Function | 1.000/Probably damaging | NA       | NA                      | 0.981    | NA                      |             |
| SNP7   | KCNJ11      | E227K    | NA       | Exon 1       | NA                              | 0.00/Affect Protein Function | 1.000/Probably damaging | −7.17583 | 0.98487                  | 0.94     | NA                      |             |
| SNP8   | KCNJ11      | L270V    | rs1800467 | Exon 1      | 11:17387284                     | 0.13/Tolerated       | 0.003/Benign             | −1.54301 | 0.18893                  | 0.566    | 0.68                    |             |
| SNP9   | KCNJ11      | I337V    | rs5215   | Exon 1       | 11:17387083                     | 0.73/Tolerated       | 0.000/Benign             | −0.89045 | 0.10817                  | 0.462    | 0.94                    |             |
| SNP10  | KCNJ11      | S385C    | rs41282930 | Exon 1     | 11:17386938                     | 0.02/Affect Protein Function | 0.380/ Possibly damaging | NA       | NA                      | 0.229    | NA                      |             |
| SNP11  | ABCC8       | G7R      | NA       | Exon 1       | NA                              | 0.00/Affect Protein Function | 1.000/ Possibly damaging | NA       | NA                      | 0.863    | NA                      |             |
| SNP12  | ABCC8       | N24K     | NA       | Exon 1       | NA                              | 0.03/Affect Protein Function | 1.000/ Possibly damaging | NA       | NA                      | 0.877    | NA                      |             |
| SNP13  | ABCC8       | F27S     | NA       | Exon 1       | NA                              | 0.00/Affect Protein Function | 0.884/ Possibly damaging | NA       | NA                      | 0.858    | NA                      |             |
| SNP14  | ABCC8       | N72S     | rs80356634 | Exon 2     | 11:17474961                     | 0.12/Tolerated       | 0.402/ Possibly damaging | NA       | NA                      | 0.802    | NA                      |             |
| SNP15  | ABCC8       | R74W     | NA       | Exon 2       | NA                              | 0.00/Affect Protein Function | 1.000/ Possibly damaging | NA       | NA                      | 0.904    | NA                      |             |
| SNP16  | ABCC8       | A116P    | NA       | NA          | NA                              | 0.12/Tolerated       | 1.000/ Possibly damaging | NA       | NA                      | 0.825    | NA                      |             |
| SNP17  | ABCC8       | E128K    | NA       | Exon 3       | NA                              | 0.02/Affect Protein Function | 1.000/ Possibly damaging | NA       | NA                      | 0.829    | NA                      |             |
| SNP18  | ABCC8       | F132L    | rs80356637 | Exon 3     | 11:17470119                     | 0.16/Tolerated       | 0.877/ Possibly damaging | NA       | NA                      | 0.847    | NA                      |             |
| SNP19  | ABCC8       | V187D    | NA       | Exon 4       | NA                              | 0.01/Affect Protein Function | 0.042/Benign           | NA       | NA                      | 0.857    | NA                      |             |
| SNP20  | ABCC8       | L213R    | rs80356642 | Exon 5     | 11:17461767                     | 0.41/Tolerated       | 0.212/ Possibly damaging | −3.12006 | 0.52998                  | 0.786    | NA                      |             |
| SNP21  | ABCC8       | E382K    | rs80356651 | Exon 10     | 11:17453151                     | 0.27/Tolerated       | 0.392/ Possibly damaging | −1.96296 | 0.26172                  | 0.872    | NA                      |             |
| SNP22  | ABCC8       | R495Q    | NA       | Exon 10     | NA                              | 0.00/Affect Protein Function | 1.000/ Possibly damaging | −8.28432 | 0.99496                  | 0.906    | NA                      |             |
| SNP23  | ABCC8       | E501K    | NA       | Exon 10     | NA                              | 0.00/Affect Protein Function | 1.000/ Possibly damaging | −2.39817 | 0.35392                  | 0.948    | NA                      |             |
Table 2 *In silico* predicted functional effects of 36 non-synonymous SNPs in the pharmacogenetics of sulfonylureas treatment by SIFT, PolyPhen-2, PANTHER, MutPred, and SNPs3D* (Continued)

| SNP   | Gene | SNP   | Exon | Predicted Function | Score   |
|-------|------|-------|------|--------------------|---------|
| SNP24 | ABCC8| L503P | NA   | Exon 10            | 0.00/Affect Protein Function |
| SNP25 | ABCC8| F686S | NA   | Exon 15            | 0.01/Affect Protein Function |
| SNP26 | ABCC8| G716V | rs72559723 | Exon 16 | 0.18/Tolerated |
| SNP27 | ABCC8| K1336N| NA   | NA                 | 0.25/Tolerated |
| SNP28 | ABCC8| L1349Q| NA   | Exon 33            | 0.01/Affect Protein Function |
| SNP29 | ABCC8| A1369S| rs757110 | Exon 33 | 0.51/Tolerated |
| SNP30 | ABCC8| S1386F| NA   | Exon 34            | 0.00/Tolerated |
| SNP31 | ABCC8| L1389P| NA   | Exon 34            | 0.00/Affect Protein Function |
| SNP32 | ABCC8| R1420C| rs28938469 | Exon 35 | 0.00/Affect Protein Function |
| SNP33 | ABCC8| I1424V| rs80356653 | Exon 35 | 0.00/Affect Protein Function |
| SNP34 | ABCC8| D1471H| NA   | Exon 36            | 0.00/Affect Protein Function |
| SNP35 | TCF7L2| P179H | rs3197486 | NA | 10:113141236 |
| SNP36 | TCF7L2| K323N | rs2757884 | NA | 10:113151761 |

*Abbreviations: MutPred Mutation Prediction, PANTHER Protein ANalysis THrough Evolutionary Relationships, PolyPhen-2 Polymorphism Phenotyping v2, SIFT Sorting Intolerant from Tolerant, SNP Single Nucleotide Polymorphism, subSPEC subStitution Position-specific Evolutionary Conservation, NA Not Available*
**Table 3** *In silico* predicted functional effects of 7 non-coding SNPs in the pharmacogenetics of sulfonylureas treatment by Haploreg v4.1, RegulomeDB, and Ensembl’s VEP*

| SNP ID | Gene Symbol | dbSNP ID | SNP Location | Chromosome Location (GRCh38.p7) | HaploReg v4.1 Motifs changed by SNP | RegulomeDB Score/Prediction | Ensembl’s VEP |
|--------|-------------|----------|--------------|---------------------------------|-----------------------------------|-------------------------------|----------------|
| SNP37  | KCNJ11      | rs5210   | 3' UTR       | 11:17386704                     | None                              | 4/Minimal binding evidence   | NA             |
| SNP38  | ABCG8       | rs1799854 | Intron 15    | 11:17427157                     | 4 altered motifs                  | 5/Minimal binding evidence   | NA             |
| SNP39  | TCF7L2      | rs7895340 | Intron 5     | 10:113041766                    | Irf, PRDM1                        | NA                           | NA             |
| SNP40  | TCF7L2      | rs7901695 | Intron 4     | 10:112994329                    | None                              | 5/Minimal binding evidence   | NA             |
| SNP41  | TCF7L2      | rs7903146 | Intron 4     | 10:112998590                    | 7 altered motifs                  | 5/Minimal binding evidence   | Risk factor    |
| SNP42  | TCF7L2      | rs11196205| Intron 5     | 10:113047288                    | SMC3                              | 5/Minimal binding evidence   | Risk factor    |
| SNP43  | TCF7L2      | rs12255372| Intron 5     | 10:113049143                    | 5 altered motifs                  | NA                           | Risk factor    |

*Abbreviations: RegulomeDB Regulome Database, SNP Single Nucleotide Polymorphism, UTR Untranslated Region, VEP Variant Effect Predictor, NA Not Available*
for DNA-binding proteins, and could have regulatory effects on gene transcription. Neither rs5210 nor rs7901695 appear to change known motifs (Table 3).

Analysis of functional consequences of SNPs by RegulomeDB RegulomeDB is a database that annotates SNPs with known and predicted regulatory elements in the intergenic regions of the human genome. Of the 7 non-coding SNPs, rs5210, rs1799854, rs7901695, rs7903146, and rs11196205 had RegulomeDB scores of 4, 5, 5, 5, and 5, respectively, which were all classified as having minimal binding evidence. Predictions were not available for either rs7895340 or rs12255372 (Table 3).

Analysis of functional consequences of SNPs by Ensembl’s VEP The Ensembl’s VEP determines the effects of genetic variants on genes, transcripts, and protein sequences, as well as regulatory regions. Three non-coding SNPs of TCF7L2 gene, i.e., rs7903146, rs11196205 and rs12255372, were predicted as risk factors (Table 3).

Discussion

Sulfonylureas are a class of drugs that stimulates insulin secretion by closing K<sub>ATP</sub> channels in pancreatic β cells. It has been estimated that 10–20% of individuals treated do not attain adequate glycemic control, and 5–10% initially responding to sulfonylurea subsequently lose the ability to maintain near-normal glycemic level [86]. This implies that genetic factors are linked with treatment efficacy of sulfonylureas. In our study, that includes 17 studies, two KCNJ11 SNPs — rs5219 (E23K) (exon 1) and rs5210 (3’-UTR), three ABCC8 SNPs — rs757110 (A1369S) (exon 33), rs1799854 (intron 15, exon 16 -3C/T), rs1799859 (R1273R) (exon 31), and two TCF7L2 SNPs rs7903146 (intron 4) and rs12255372 (intron 5) have been associated with response to sulfonylureas. Based on bioinformatics predictions for 36 selected coding SNPs (all are missense) for KCNJ11, ABCC8, and TCF7L2, by applying a set of computational tools — SIFT, PolyPhen-2, PANTHER, MutPred, and SNPs3D. Our bioinformatics prediction results demonstrated that 8 KCNJ11 missense SNPs (R27H, V59M, I182V, R192H, R201H, E227K, L270V, and S385C), 23 ABCC8 missense SNPs (G7R, N24K, F27S, N72S, R74W, A116P, E128K, F132L, V187D, L213R, E382K, R495Q, E501K, L503P, F686S, G716V, K1336N, L1349Q, S1386F, L1389P, R1420C, I1424V, D1471H), and 2 TCF7L2 missense SNPs (P179H, K323N) could affect protein functions with SIFT score ≤ 0.05, or PolyPhen-2 score ≥ 0.85, or PANTHER subSPEC score ≤ −3, or MutPred > 0.5, or SNPs3D score < 0. Of them, previous studies showed that mutant alleles of 4 KCNJ11 missense SNPs (R27H, V59M, R192H, and R201H) and 5 ABCC8 missense SNPs (G7R, N24K, F27S, R74W, and E128K) can be successfully rescued by sulfonylurea treatments. In addition, 3 TCF7L2 non-coding SNPs — rs7903146, rs11196205 and rs12255372 were predicted as risk factor based on Ensembl’s VEP, although their functional impacts in sulfonylurea results need to be elucidated by further experimental studies.

Conclusion

The ultimate goal of pharmacogenetics is the development of personalized medicine through individual genetic profiles which would accurately predict which individuals with a specific medical condition would respond to a specific medical therapy. Traditional medicine refers to the broad application of “standard of care” or “one-size-fits-all” treatments to all patients with a given diagnosis. In contrast, personalized medicine, often described as providing “the right drug for the right patient at the right dose and time” [87], tailors medical treatment according to each patient’s personal history, genetic profile and/or specific biomarkers [88, 89]. Therefore, the full application of personalized medicine in health care will require significant changes in regulatory and reimbursement policies as well as legislative protections for privacy. The U.S. Food and Drug Administration has updated the labels of more than 120 drugs with recommendations for genetic testing prior to their use [90]. Currently, most genetic testing is based on genotypic effects. Haplotypes of multiple linked genetic variants provide more precise information of their functional impacts than individual genetic markers [91, 92], which could also be potentially important for diagnosis and prognosis [93]. In future, regulatory authorities shall formulate clear guidelines for evaluating and approving personalized diagnostics and therapeutics and identify patients who can benefit from them.

Abbreviations

ABCC8: ATP Binding Cassette Subfamily C; Member 8; ADP: Adenosine diphosphate; ATP: Adenosine triphosphate; CAMP: Cyclic adenosine monophosphate; CL: cytosolic loop; dbSNP: Single Nucleotide Polymorphism database; EnBase: Excerpta Medica Database; Glp-1: Glucagon-like peptide-1; HbA1C: Glycated hemoglobin A1C; Go-DARTS: Genetics of Diabetes Audit and Research Study in Tayside Scotland; KATP: ATP-sensitive K<sub>+</sub> channel; KCNJ11: Potassium channel, inwardly rectifying subfamily J, member 11; Kir: Inwardly rectifying K<sub>+</sub> channel; Lef: Lymphocyte enhancer factor; MutPred: Mutation prediction; NBD: nucleotide binding domain; NCBi: National Center for Biotechnology Information; nSNP: Non-synonymous single nucleotide polymorphism; PANTHER: Protein analysis through evolutionary relationships; PRA: Protein kinase A; PolyPhen-2: Polymorphism phenotyping v2; RCT: Randomized clinical trial; RegulomeDB: Regulome database; SIFT: Sorting Intolerant from Tolerant; SNP: Single nucleotide polymorphism; SU: Sulfonylurea; subSPEC: substitution Position-specific Evolutionary Conservation; SUR: Sulfonylurea receptor; T2D: Type 2 diabetes; TCF: T-cell factor; TCF7L2: T-cell factor 7-like 2; TMD: transmembrane domain; UKPD: United Kingdom Prospective Diabetes Study; UTR: Untranslated region; VEP: Variant effect predictor; WHO-MONICA: World Health Organization-Multinational MONitoring of trends and determinants of cardiovascular diseases; Wt: Wildtype type

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TN conceived the idea for the project. TN and JS contributed to study design and conception. JS, YY and TN participated in data analysis and interpretation. JS, YY and TN drafted the manuscript. FMJ and YW revised it critically for intellectual content. All authors read and approved the final version of the manuscript.

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