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Variation in *KCNQ1* is associated with therapeutic response to sulphonylureas

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
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Summary

Background: We aimed to analyse quantitative effects of treatment with sulphonylurea in addition to metformin on parameters of glycemic control in relation to *KCNQ1* genotypes, and to identify factors predictive for the response to sulphonylurea treatment.

Material/Methods: Effect of 6-month sulphonylurea therapy in addition to metformin on glycemic control according to *KCNQ1* genotypes was evaluated in 87 patients with type 2 diabetes who failed to achieve glycemic control on metformin monotherapy. *KCNQ1* rs163184 (T>G) polymorphism was determined by real-time PCR with melting analysis of unlabeled probe.

Results: The reduction in fasting plasma glucose (ΔFPG) after 6-month sulphonylurea therapy significantly differed among 3 *KCNQ1* genotype groups (ANOVA, p=0.017). In a recessive genetic model, carriers of the T-allele (TT+TG) achieved significantly lower FPG levels in comparison with patients with the GG genotype (6.95±0.13 *vs.* 7.50±0.21 mmol/L, p=0.033). Consequently, ΔFPG was significantly higher in the TT+TG group compared to the GG group (1.58±0.13 *vs.* 1.04±0.18 mmol/L, p=0.016). In multiple linear regression analysis *KCNQ1* genotype (p=0.016) and baseline FPG (p<0.001) were the only significant independent predictors of ΔFPG (R^2=0.48).

Conclusions: Our results suggest that the magnitude of FPG reduction after 6-month sulphonylurea treatment in addition to metformin in patients with type 2 diabetes is related to the variation in *KCNQ1*. The FPG response to sulphonylureas was significantly lower in carriers of the risk GG genotype.

key words: **pharmacogenetics • sulphonylureas • *KCNQ1* • glycemic control • type 2 diabetes**

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Background

Type 2 diabetes is a disease with significant genetic predisposition. In recent years almost 40 genes associated with type 2 diabetes have been identified by genome-wide association studies [1]. Among them, 2 independent genome-wide studies in East Asian populations reported that several polymorphisms of potassium voltage-gated channel KQT-like subfamily member 1 (*KCNQ1*) gene were consistently associated with type 2 diabetes [2,3]. This association was subsequently replicated in several population cohorts of Asian and European ancestry [4–7].

KCNQ1 gene encodes the pore-forming subunit of a voltage-gated K^+ channel (KvLQT1) that plays a key role in the repolarization of the cardiac action potential, as well as water and salt transport in epithelial tissues [8,9]. Both human and animal studies suggest that mutations in *KCNQ1* can result in the K^+ channel dysfunction and cause the hereditary long QT syndrome and familial atrial fibrilation [10,11]. *KCNQ1* is also expressed in pancreatic islets and insulin-secreting cell lines [2,3,12]. Several studies indicated that various *KCNQ1* polymorphisms were related either to impaired insulin secretion [6,7,13–15] or to impaired incretin secretion [15].

The recommended initial therapeutic interventions in type 2 diabetes include lifestyle changes and pharmacotherapy with metformin [16]. In patients with metformin monotherapy failure, sulphonylureas are frequently used as a second-line treatment. Sulphonylureas act as insulin secretagogues through the stimulation of insulin secretion via the sulfonylurea receptor 1 in pancreatic β-cells [17]. Considerable interindividual variation in the hypoglycaemic response to sulphonylureas likely reflects variations in the β-cell secretory reserve, and may relate to variations in genes involved in regulating β-cell function [18–21].

Since genetic variation in *KCNQ1* is associated with fasting glucose and β-cell function [13], we hypothesised that the magnitude of sulphonylurea treatment effect might be related to the *KCNQ1* genotype. Therefore, the aim of the present pharmacogenetic pilot study was to analyse quantitative effects of treatment with sulphonylurea in addition to metformin on parameters of glycaemic control with respect to *KCNQ1* genotypes in patients with type 2 diabetes.

Material and Methods

Patients

Patients with type 2 diabetes diagnosed according to the American Diabetes Association criteria [22] recruited from 3 out-patient clinics participated in the study, which was conducted in a university hospital setting. Patients were eligible for the study if they were on previous metformin monotherapy for at least 6 months, and failed to maintain HbA_{1c} <7.0% on maximal tolerated doses of metformin at 2 consecutive visits within a 3-month period. Inclusion criteria were HbA_{1c} of 7.0–11.0%, fasting glycaemia of 6–15 mmol/L, age 35–70 years, and BMI 20–35 kg/m^2. Patients with malignancies, hypothyroidism, chronic renal failure, severe liver disease, systemic inflammatory disease, and receiving corticosteroid treatment were excluded. The study was approved by the L. Pasteur University Hospital Review Board, and all subjects gave written consent to participate in the study.

Anthropometric data and diabetes duration were recorded at the baseline visit. Blood samples were taken for biochemical measurements of FPG, HbA_{1c}, lipid levels and genotyping. Sulphonylurea treatment was started with gliclazide, glimepiride, glipizide or glibenclamide. Sulphonylurea dose could have been adjusted after 3 months based on blood glucose self-monitoring results. Measurements of body weight, FPG, HbA_{1c} and serum lipids were repeated after 6 months following initiation of sulphonylurea therapy.

Biochemical analyses

In all patients, peripheral venous blood samples were collected between 7–8 a.m. following an overnight 12-hour fast. Glucose was measured by glucose oxidase method, and cholesterol, triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol were measured by routine enzymatic methods (Pliva-Lachema, Czech Republic) on a Beckman autoanalyser. HbA_{1c} was measured using an immunoturbidimetric method (Roche Diagnostica, France).

Genotyping of *KCNQ1* rs163184 (T>G)

Genomic DNA was extracted using a Wizard Genomic DNA purification kit (Promega Corp., Wisconsin, USA). PCR was performed in 10 µl of reaction volume on a LightScanner 32 instrument (Idaho Technology Inc., Salt Lake City, USA) at asymmetric primer ratio (1:10). Master mix was composed of 1x LCGreen Plus+ (Idaho Technology Inc.), 200 µM dNTPs (Jena Bioscience, Jena, Germany), 0.06 µM forward primer, 0.6 µM reverse primer, 1.2 µM unlabeled blocked probe, 3 mM $MgCl_2$, 250 µg/ml BSA (Fermentas, Burlington, Canada), 0.5M betaine (Sigma-Aldrich, Germany), 1 U BioThermAB polymerase with 1x corresponding buffer (GeneCraft, Munster, Germany), and approximately 10 ng DNA. The sequences of oligonucleotides (Sigma-Aldrich, Germany) were:

CTTTGCTCAGTAACGGACTGGACCA (forward primer), TCTGTGGAAAGGGGTTGCCCTGC (reverse primer), and TGGAGTTTGGAGTAAAGAGAGA-phos (probe).

PCR conditions were the following: initial denaturation at 95°C for 5 min, 60 cycles at 95°C for 10 s, 56°C for 15 s and 72°C for 15 s. Amplification was performed at the thermal transition rate of 10°C/s for all steps, and was immediately followed by melting analysis with a denaturation at 95°C for 30 s and renaturation at 45°C for 1 minute. Data were acquired over a 45–90°C range at the thermal transition rate of 0.1°C/s. Genotypes were identified by the melting temperatures indicated by peaks on the derivate plots after normalization using LightScanner 32 software 1.0.0.23 (Idaho Technology Inc.). The probe was designed to exactly match the allele T. The T allele homozygotes had a derivative melting peak at 60°C and G allele homozygous samples had a melting peak at 53°C, whereas heterozygotes showed both peaks.

Statistical analyses

Statistical analyses were performed using SPSS 17.0 for Windows software (SPSS Inc., Chicago, IL, USA). Relative

Table 1. Baseline characteristics of the subjects and the effect of 6-month sulphonylurea treatment in addition to previous metformin monotherapy in the entire group of patients.

	Before treatment	After treatment	*p*
Weight (kg)	84.0±1.8	84.3±1.9	0.228
BMI (kg/m^2)	30.4±0.4	30.5±0.4	0.605
FPG (mmol/L)	8.47±0.14	7.12±0.11	< 0.001
HbA_{1c} (%)	7.98±0.10	6.97±0.06	< 0.001
Cholesterol (mmol/L)	5.03±0.15	4.90±0.15	0.472
LDL cholesterol (mmol/L)	2.74±0.13	2.64±0.10	0.542
HDL cholesterol (mmol/L)	1.20±0.05	1.22±0.05	0.588
Triglycerides (mmol/L)	2.07±0.12	1.86±0.13	0.036

Data are expressed as mean ±SE. *p*-values refer to Student's tests. BMI – body mass index; FPG – fasting plasma glucose; LDL – low-density lipoprotein; HDL – high-density lipoprotein.

frequencies of sexes were compared using the χ^2-test. Continuous variables are presented as mean ± standard error of mean (SE). For comparison of means, either unpaired Student's t-test or analysis of variance (ANOVA) was used. General linear models and multiple linear regression analyses were used to account for baseline differences and other confounding factors for the 2 primary outcomes – change in FPG (ΔFPG) and HbA_{1c} (ΔHbA_{1c}) after treatment. All models were adjusted for age, sex, BMI, and either for baseline FPG or baseline HbA_{1c} values.

Results

The effect of 6-month treatment with sulphonylureas in the whole study group is shown in Table 1. Mean HbA_{1c} level decreased by 1.0%, mean FPG by 1.5 mmol/L, and mean triglyceride levels by 0.3 mmol/L (p<0.001, p<0.001, p=0.036, respectively). In contrast, no significant differences were recorded in body weight, BMI, total cholesterol, LDL cholesterol and HDL cholesterol after sulphonylurea treatment.

The distribution of *KCNQ1* rs163184 genotypes followed Hardy-Weinberg equilibrium (p=0.39). Twenty subjects were homozygous for the T-allele (TT genotype), 39 were carriers of 1 risk G-allele (TG genotype), and 28 were homozygotes for the G-allele (GG genotype).

Baseline clinical and biochemical characteristics, as well as the indices of glycaemic control after sulphonylurea treatment of 3 genotype groups are displayed in Table 2. No significant differences were observed in sex representation, age, weight, BMI, diabetes duration, cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and either baseline FPG or HbA_{1c} levels among the genotype groups.

The reduction in FPG (ΔFPG) after 6-month sulphonylurea therapy significantly differed among the 3 *KCNQ1* genotype groups (ANOVA, p=0.017). The post-hoc analysis revealed greater ΔFPG in the TG compared to the GG genotype group (p=0.015) (Table 2).

In further analyses, a recessive genetic model was tested in which carriers of the T-allele were pooled (TT+TG) and compared with patients with the GG genotype (Table 3). After sulphonylurea therapy, patients in the TT+TG group achieved significantly lower FPG levels in comparison with patients with the GG genotype (6.95±0.13 *vs.* 7.50±0.21 mmol/L, p=0.033). Consequently, ΔFPG was significantly higher in the TT+TG group compared to the GG group (1.58±0.13 *vs.* 1.04±0.18 mmol/L, p=0.016) (Table 3).

In multiple linear regression analysis with ΔFPG as a dependent variable and *KCNQ1* genotype, age, sex, BMI, and baseline FPG as independent variables, *KCNQ1* genotype (p=0.016) and baseline FPG (p<0.001) were the only significant independent predictors of ΔFPG (R^2=0.48).

Discussion

In the present study we have shown that the homozygous carriers of the risk G-allele of the *KCNQ1* rs163184 gene polymorphism responded to treatment with sulphonylurea by significantly lower reduction in fasting glycaemia. In multivariate analysis, *KCNQ1* genotype and baseline FPG levels were the only independent significant predictors of FPG reduction after sulphonylurea treatment.

The reports on the potential relationships between the effect of sulphonylurea therapy and genes variants associated with type 2 diabetes are scarce. Sulphonylurea receptor 1 is encoded by ATP-binding cassette transporter sub-family C member 8 (*ABCC8*) gene. A recent study in 115 Chinese patients revealed that carriers of the risk Ala-allele in the non-synonymous *ABCC8* Ser1369Ala polymorphism were more sensitive to gliclazide treatment with respect to reduction of HbA_{1c} level in comparison with Ser/Ser homozygotes [18]. This finding was confirmed in a larger study of 1268 Chinese subjects with type 2 diabetes, in which 8-week treatment with gliclazide showed higher therapeutic efficacy on fasting glycemia, but not on HbA_{1c} levels, observed in patients with Ala/Ala genotype when compared with patients with Ser/Ser genotype [19].

The Genetics of Diabetes Audit and Reasearch Tayside Study (GoDARTS) was another robust pharmacogenetic study which addressed the relationship between 2 transcription

Table 2. Clinical and biochemical characteristics of the subjects according to *KCNQ1* rs163184 genotypes.

	TT (n=20)	TG (n=39)	GG (n=28)	*p*
Gender (males/females)	11/9	20/19	11/17	0.491*
Age (years)	63.7±2.2	61.8±1.6	63.8±1.9	0.683
Diabetes duration (years)	5.7±0.8	6.4±0.5	5.7±0.6	0.641
Weight (kg)	83.9±3.9	84.8±2.8	83.8±3.0	0.960
BMI (kg/m^2)	29.8±0.8	30.9±0.6	30.3±0.7	0.513
FPG (mmol/L) – baseline	8.20±0.32	8.67±0.23	8.60±0.27	0.465
FPG (mmol/L) – after treatment	7.11±0.25	6.87±0.18	7.50±0.21	0.076
ΔFPG (mmol/L)	1.31±0.22	1.72±0.15**	1.04±0.18	0.017
HbA_{1c} (%) – baseline	7.84±0.20	8.07±0.14	7.96±0.17	0.640
HbA_{1c} (%) – after treatment	6.90±0.13	6.96±0.10	7.06±0.11	0.632
ΔHbA_{1c} (%)	1.04±0.11	1.05±0.08	0.92±0.09	0.523
Total cholesterol (mmol/L)	4.94±0.20	5.38±0.14	5.25±0.18	0.209
LDL cholesterol (mmol/L)	2.74±0.14	2.85±0.10	2.71±0.13	0.684
HDL cholesterol (mmol/L)	1.14±0.06	1.13±0.04	1.11±0.06	0.911
Triglycerides (mmol/L)	2.11±0.16	2.04±0.11	2.23±0.14	0.590

Data are expressed as mean ±SE. * *p* refers to χ^2-test, otherwise *p* refers to ANOVA. ΔFPG and ΔHbA1c means were adjusted in general linear models for gender, age, BMI and baseline FPG or HbA1c values, respectively. ** *p*=0.015 for comparison TG *vs.* GG (Bonferroni test). BMI – body mass index; FPG – fasting plasma glucose; LDL – low-density lipoprotein; HDL – high-density lipoprotein.

Table 3. Effect of sulphonylurea treatment on glycemic control with respect to *KCNQ1* genotypes: recessive model.

	TT+TG (n=59)	GG (n=28)	*p*
FPG (mmol/L) – baseline	8.51±0.19	8.60±0.27	0.785
FPG (mmol/L) – after treatment	6.95±0.14	7.50±0.21	0.033
ΔFPG (mmol/L)	1.58±0.13	1.04±0.18	0.016
HbA1c (%) – baseline	7.99±0.12	7.96±0.17	0.892
HbA1c (%) – after treatment	6.93±0.08	7.06±0.11	0.375
ΔHbA1c (%)	1.05±0.06	0.92±0.09	0.255

Data are displayed as mean ±SE, *p*-values refer to Student's tests. ΔFPG and ΔHbA_{1c} means were adjusted in general linear models for gender, age, BMI, and baseline FPG or HbA_{1c} values, respectively. BMI – body mass index; FPG – fasting plasma glucose; LDL – low-density lipoprotein; HDL – high-density lipoprotein.

factor 7-like 2 (*TCF7L2*) polymorphisms and the response to sulphonylurea therapy in type 2 diabetic patients. In that study, 901 Scottish patients with type 2 diabetes treated with sulphonylurea were analysed. The probability for early sulphonylurea treatment failure was almost doubled in subjects with the risk TT genotypes of both rs12255372 and rs7901346 polymorphisms compared to those homozygous for the reference non-risk genotypes [20]. Furthermore, our recent study demonstrated that carriers of the risk T-allele of *TCF7L2* rs7903146 polymorphism responded to treatment with sulphonylurea by significantly smaller reductions in HbA_{1c} and FPG levels in comparison with patients with the CC genotype [21].

In the present study we observed a significant association between the *KCNQ1* rs163184 gene polymorphism and the efficacy of sulphonylurea treatment in type 2 diabetic patients who failed to achieve adequate glycaemic control on monotherapy with metformin – patients carrying 2 risk G-alleles of *KCNQ1* (GG genotype) had significantly smaller

reductions in FPG levels after 6-month therapy than those with at least 1 non-risk T-allele (TT+TG genotypes). The differences in mean FPG (0.54 mmol/l) observed between different genotypes of *KCNQ1* rs163184 polymorphism after sulphonylurea treatment in the present report were similar to those observed for *TCF7L2* polymorphism [21]. To our best knowledge the present findings are the first to provide evidence of differences in the FPG reductions between various *KCNQ1* genotype groups. Nevertheless, similar to Feng et al who analysed the treatment effect with respect to *ABCC8* genotypes [19], we did not observe significant effect of the *KCNQ1* rs163184 gene polymorphism on ΔHbA_{1c} following sulphonylurea treatment.

Besides the *KCNQ1* genotype, baseline FPG also independently predicted the FPG reduction after sulphonylurea therapy. Importantly, the effect of *KCNQ1* gene polymorphism on the reduction in FPG was independent of the baseline FPG levels in the present study.

The mechanism underlying the effects of *KCNQ1* polymorphism on the therapeutic effect of sulphonylureas is poorly understood. In a physiological study in INS-1 cell cultures, the blockade of the KvLQT1 channel with KCNQ1 protein inhibitor 293B stimulated insulin secretion in the presence of sulphonylurea drug tolbutamide [12], suggesting that KvLQT1 channels might play a role in fine-tuning of insulin secretion during sulphonylurea treatment.

There are limitations in the current pilot study, such as the small size of the study group. However, the approximately 35% difference in ΔFPG after 6-month therapy between the carriers of risk GG genotype and the carriers of non-risk T-allele suggests that the sample size of this study, although limited, is enough to gain understanding on the role of *KCNQ1* gene polymorphisms in the pharmacologic response to sulphonylureas. Furthermore, although the duration of the present study was longer than the previous ones [18,19], our results reflect only the effect of sulphonylurea therapy during the first 6 months after initiation of this treatment; therefore, our results cannot be automatically extrapolated beyond this period. Nevertheless, in the GoDARTS study, higher probability of sulphonylurea failure was observed up to 12 months following initiation of therapy in patients with the risk *TCF7L2* genotypes [20]. Therefore, the *KCNQ1* genotype-related differences in glucose lowering response to sulphonylureas observed in the present study might be preserved beyond 6 months. Further studies are needed to address this question. Importantly, investigation of a homogenous group of patients with type 2 diabetes, in whom sulphonylurea was started in a typical clinical situation after metformin monotherapy failure with mean HbA_{1c} level of approximately 8% represents a strength of the present study.

Conclusions

The present study showed for the first time that the variation in *KCNQ1* gene is related to therapeutic response to sulphonylurea treatment in addition to previous metformin monotherapy. Large-scale pharmacogenetic studies are needed to examine combined effect of risk alleles of several genes and their eventual interactions on response to sulphonylureas. Such observations might lead to the development of genotype-based personalized strategies for the treatment of type 2 diabetes in the future.

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