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The Ser1369Ala variant of *ABCC8* and the risk for severe sulfonylurea-induced hypoglycemia in German patients with Type 2 diabetes

A letter in response to: Sato R, Watanabe H, Genma R *et al.* *ABCC8* polymorphism (Ser1369Ala): influence on severe hypoglycemia due to sulfonylureas. *Pharmacogenomics* 11(12), 1743–1750 (2010).

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We read with interest the Preliminary Communication by Sato *et al.* [1], who reported no influence of the Ser1369Ala variant of the *ABCC8* gene on the risk of severe hypoglycemia (SH) upon glimepiride and glibenclamide treatment in Japanese patients with Type 2 diabetes (T2D).

SH is a life-threatening and often misdiagnosed condition resulting in an increased mortality of up to 10% [2,3]. Age, multimorbidity, duration of T2D, renal impairment, polypharmacy and low HbA1c values are established predictors for SH. However, not every patient treated with sulfonylureas develops SH despite the presence of multiple risk factors. It can therefore be postulated that pharmacogenetic factors could play a role in the complex etiology of SH. Since SH may increase cardiovascular and all-cause mortality [4], prediction and prevention of SH appear crucial in the antidiabetic therapy. Thus, knowledge of pharmacogenetic aspects in regard to the response to sulfonylureas might contribute to improved life quality and increased life expectancy in patients with T2D.

ATP-sensitive K⁺ (KATP) channels in pancreatic β -cells are composed of the Kir6.2 and SUR1 subunits and they are encoded by the *KCNJ11* and *ABCC8* genes, respectively. Based on their role in insulin secretion, they represent plausible candidate genes whose functional polymorphisms might affect the response to sulfonylureas. Sato *et al.* hypothesized that the Ser1369Ala variant of the sulfonylurea receptor gene *ABCC8* affects the response to sulfonylureas in patients with T2D and so, results in reduced risk of SH [1]. By including 32 Japanese patients with T2D admitted to the hospital with SH and 125 consecutive T2D outpatients without SH, they did not observe an effect of the Ser1369Ala variant on SH due to glimepiride or glibenclamide [1]. Given the known genetic as well as pharmacogenetic heterogeneity between populations and the rather small sample size

in the reported study, we investigated whether the Ser1369Ala variant might reduce the risk of SH in German–Caucasians. We genotyped the Ser1369Ala variant in 111 German patients with T2D admitted to the emergency department as a result of SH and a control group of 100 patients with T2D but without a history of SH. The patients were recruited between 1 January 2000 and 31 December 2010 at the medical department of the Klinikum Lippe-Detmold in East Westphalia, Germany. All of the patients were treated with sulfonylurea agents; 50 of them had also been treated with insulin. SH was defined restrictively as a symptomatic event requiring treatment with intravenous glucose and was confirmed by a blood glucose measurement of <50 mg/dl (<2.8 mmol/l). Patients in the control group had also been receiving sulfonylureas, but had not experienced any SH. This control group included similarly aged, multimorbid and pretreated diabetic individuals. The patients in this group had been treated with the sulfonylurea drugs glimepiride (n = 80), glibenclamide (n = 18) and gliquidone (n = 2). In the group of cases with SH, 82 patients received glimepiride, 28 received glibenclamide and only one patient required gliquidone. In addition to sulfonylureas, some patients had been treated with metformin. Metformin treatment was comparable in both the control and the case group (43 vs 43 subjects, respectively). The protocol was approved by the Ethics Committee of the University of Münster School of Medicine (Münster, Germany) and by the Ethics Committee of the University of Leipzig School of Medicine (Leipzig, Germany). All patients gave written informed consent to participate in the study.

The study subjects were genotyped using the TaqMan allelic discrimination assay (Assays-on-Demand™, Applied Biosystems, Inc., CA, USA). The genotype distribution was consistent with Hardy–Weinberg equilibrium ($p = 0.96$).

Table 1. Clinical characteristics of all participants.

	Control group	Patients with severe hypoglycemia	p-value
Sex (male/female)	n = 100 51/49	n = 111 49/62	0.32 [†]
Age (year)	79.42 ± 9.15	77.22 ± 9.57	0.09
BMI (kg/m ²)	26.87 ± 4.28	26.50 ± 5.44	0.59
Serum creatinine (mg/dl)	1.71 ± 1.03	1.53 ± 0.83	0.17
Creatinine clearance (ml/min)	37.96 ± 18.13	45.74 ± 23.08	0.02
HbA1c (%)	7.17 ± 1.34	6.55 ± 1.14	<0.001
Age at onset of diabetes (years)	67.85 ± 12.04	66.29 ± 11.97	0.36
Diabetes duration (years)	11.29 ± 8.11	10.81 ± 9.54	0.70
Sulfonylurea dose			
– Glibenclamide	5.03 ± 3.60 (n = 18)	6.19 ± 3.69 (n = 28)	0.29
– Glimepiride	2.31 ± 1.34 (n = 80)	2.84 ± 1.58 (n = 82)	0.02
– Gliquidon	60.0 ± 0.00 (n = 2)	30.0 ± 0.00 (n = 1)	–
Comedication (number of all drugs)	7.31 ± 2.68	6.88 ± 2.78	0.26
Metformin treatment (number of patients)	43	43	0.53 [†]

Data are mean ± standard deviation; p-values for comparisons between genotypic groups by t-test statistics.
[†]χ² test.

Genotyping success rate was 99%, and duplicate genotyping concordance was 100%.

The clinical characteristics of all study participants are shown in TABLE 1. Briefly, the T2D patients with SH were on average 2 years younger and had higher creatinine clearance and lower HbA1c than patients without SH. The comedication summarized as number of all drugs taken by the patients was comparable between cases and controls (TABLE 1).

In the univariate logistic regression analyses including age, gender, HbA1c, diabetes duration, sulfonylurea dose and genotype, lower HbA1c appeared to be the only predictor of SH (odds ratio [OR]: 1.53; 95% CI: 1.19–2.00). There was no significant difference in the frequency of the Ala allele between the control group and the cases with SH (43 vs 38%; $p = 0.27$ and $p = 0.29$ adjusted for HbA1c as the only predictor of SH; OR: 0.80 [0.54–1.19] in an additive mode of inheritance) (TABLE 2). In addition, the Ser1369Ala variant did not affect HbA1c levels

(6.98 ± 1.37 for Ser/Ser vs 6.63 ± 1.09 for Ser/Ala vs 7.23 ± 1.47 for Ala/Ala carriers; $p = 0.60$; adjusted for age, sex, BMI, diabetes duration and sulfonylurea dose).

Although our data in German subjects are consistent with those from Japan [1], there are several differences that should be mentioned. In the study by Sato *et al.*, the patients with SH were carefully selected excluding explicitly those with severe comorbidities, in particular renal impairment or heart failure. Thus, the conditions of real life were not reflected as the typical patient with SH is characterized by multimorbidity [2]. In our present study, we chose an alternative approach by including all consecutive subjects with SH, irrespective of comorbidities. It is also noteworthy that despite the relatively small sample size in our cohort, we still had 80% power (at $\alpha = 0.05$) to detect an effect with OR of 1.7, while the study by Sato *et al.* would require an OR of 2.2 to be detectable under similar conditions (calculated by Quanto [101]). Therefore, although both studies indicate no effect of the variant on SH, smaller effects could have been missed due to the limited statistical power. Thus, further studies are warranted to ultimately confirm these data. Finally, it is of note that despite known genetic, as well as pharmacogenetic, heterogeneity between Japanese and German–Caucasian populations, there was no difference in frequency of the Ala variant (43% in the controls) between our study and that reported by Sato *et al.* [1].

Table 2. Frequency of Ser1369Ala genotypes in controls and cases.

Allele	Controls (T2D without SH), n (%)	Cases (T2D with SH), n (%)	p-value
Ser/Ser	32 (32.0)	42 (38.2)	–
Ser/Ala	50 (50.0)	53 (48.2)	0.27
Ala/Ala	18 (18.0)	15 (13.6)	–

p-value was calculated in logistic regression analysis in additive mode of inheritance.
SH: Severe hypoglycemia; T2D: Type 2 diabetes.

In conclusion, our data suggest that the Ser1369Ala variant in *ABCC8* does not affect the response to sulfonylurea treatment and so, is not a major player in the etiology of SH in German patients with T2D.

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Disclaimer

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the

principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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