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Pharmacogenetics of Hypoglycemia Associated with Sulfonylurea Therapy in Usual Clinical Care

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Abstract

Hypoglycemia is a common complication among type 2 diabetes mellitus (T2DM) patients receiving sulfonylurea therapy. The aim of this study was to determine if genetic contributions to sulfonylurea pharmacokinetics or pharmacodynamics substantially affect the risk of hypoglycemia in these patients. In a retrospective case-control study in European American patients with T2DM, we examined the potential association between *CYP2C9* reduced function variants and sulfonylurea-related hypoglycemia. We also explored the relationship between sulfonylurea-related hypoglycemia and several candidate genetic variants previously reported to alter the response to sulfonylureas. We detected no evidence of association between *CYP2C9* reduced function alleles or any of the candidate genetic variants and sulfonylurea-related hypoglycemia. In conclusion, we identified no clinically significant predictors of hypoglycemia among genes associated with sulfonylurea pharmacokinetics or pharmacodynamics.

Introduction

Type 2 diabetes mellitus (T2DM) affects more than 285 million people worldwide, including 25 million (~8% of the population) in the United States[1]. Sulfonylureas are a class of oral antidiabetic agent widely used for management of T2DM[2]. In the United States, approximately 18–25% of patients with T2DM receive a sulfonylurea for initial therapy[3]. Sulfonylureas lower blood glucose by stimulating insulin release from pancreatic beta cells.

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Conflict of Interest

The authors declare no conflicts of interest.

Consequently, patients with T2DM receiving sulfonylurea therapy are at risk for hypoglycemia, which can have serious consequences[4]. In addition to being a common life-threatening complication, hypoglycemia adversely affects quality of life and adherence to therapy in patients with T2DM[5,6]. Furthermore, it is associated with increased overall and cardiovascular mortality[7]. Accordingly, the American Diabetes Association has indicated that reducing hypoglycemia is a key goal of therapy[6].

Among individual patients, the response to sulfonylureas and the risk of hypoglycemia varies markedly[8]. Since the risk of hypoglycemia associated with sulfonylurea therapy increases with higher drug concentration, genetic variation affecting drug clearance and efficacy may contribute to interindividual variability in risk. The most commonly used sulfonylureas, including the second-generation agents glyburide, glipizide, and glimepiride, are metabolized by the cytochrome P450 (CYP) 2C9 enzyme[9]. Two common, well-characterized *CYP2C9* genetic variants that result in amino acid substitutions, *CYP2C9**2 (Arg144Cys) and *CYP2C9**3 (Ile359Leu), encode a CYP2C9 enzyme with decreased activity[9,10]. These genetic variants are associated with increased concentrations of several CYP2C9 substrate drugs, including sulfonylureas[10]. In individuals homozygous for *CYP2C9* *2 or *3 variants, the clearance of sulfonylureas such as glyburide is between 50% and 80% of that of individuals with *CYP2C9* *1 alleles[10]. Patients carrying *CYP2C9* decreased function variants could be at increased risk for sulfonylurea-related hypoglycemia. Additionally, multiple genes affect the response to sulfonylureas (pharmacodynamics)[8,11,12], and several studies have reported associations between sulfonylurea efficacy and variants in a number of genes[11–22]. However, few studies have investigated the association between variation in these genes and sulfonylurea-related hypoglycemia[23–26].

Should genetic determinants of sulfonylurea pharmacokinetics or pharmacodynamics substantially affect the risk of hypoglycemia, patients at increased risk could be identified by preemptive genotyping. Those patients at increased risk could be prescribed lower doses of sulfonylureas or alternative drugs, thereby potentially avoiding hypoglycemic episodes. Given the relative lack of information regarding the genetic contribution to sulfonylurea-related hypoglycemia[8,12,27], we examined the potential association between *CYP2C9* variants and hypoglycemia in T2DM patients receiving sulfonylurea therapy. Additionally, we explored the relationship between sulfonylurea-related hypoglycemia and candidate genetic variants previously reported to alter response to sulfonylureas. However, since there is strong evidence linking *CYP2C9* genetic variants to sulfonylurea pharmacokinetics, and weaker evidence for an impact of variants in other genes on sulfonylurea effects, a more detailed analysis of the *CYP2C9* variants was performed.

Methods

Study design

We performed a retrospective case-control study using the Vanderbilt University Medical Center DNA repository, BioVU, which is linked to a de-identified version of the electronic medical record (dEMR)[28]. The Institutional Review Board of Vanderbilt University Medical Center approved the study.

Study population

Using bioinformatics algorithms in the dEMR (Figure 1), we selected European American (EA) and African American (AA) adults (≥18 years) with T2DM that were prescribed a second-generation sulfonylurea (glyburide, glipizide, glimepiride) (Supplementary Table 1). For each patient, the date of the first recorded use of a sulfonylurea was termed t_0. Patients using insulin at t_0 or during the three months preceding it were excluded from the study. Additional exclusion criteria included cancer of the liver, pancreas, or kidney. For each patient, the study period continued from t_0 until the first occurrence of any of the following: three months without mention of a sulfonylurea in the dEMR, initiation of insulin therapy, death, or 12 months after t_0.

Definition of cases and controls

Individuals with potential hypoglycemic events were captured using three strategies: 1) laboratory blood glucose values <70 mg/dL[6], 2) ICD9/10 codes for hypoglycemia (Supplementary Table 2), and 3) a free text search for key terms indicating possible hypoglycemia (Supplementary Table 3). The dEMRs of all potential cases of hypoglycemia were reviewed to identify those who met the outcome definition of hypoglycemia; cases were defined as those patients that experienced at least one episode of hypoglycemia in the study period. Hypoglycemic events occurring in the setting of an underlying serious medical event or illness (e.g. surgery, receiving parenteral nutrition, palliative care) were excluded. Potential controls were individuals meeting study inclusion criteria who had no evidence of hypoglycemia. A subset of controls was reviewed to confirm algorithm accuracy. Finally, we performed frequency-matching of confirmed cases with controls at a ratio of 1:3 based on race, sex, and age at first sulfonylurea mention (calculated based on year of birth ±2 years and year of t_0 ±2 years).

Outcome

The primary outcome was occurrence of hypoglycemia which included all the American Diabetes Association categories: severe hypoglycemia (an event requiring the assistance of another person to administer carbohydrate or other resuscitative actions), documented symptomatic hypoglycemia (typical symptoms of hypoglycemia accompanied by a measured plasma glucose concentration <70 mg/dl), probable symptomatic hypoglycemia (plasma glucose was not measured but the symptoms of hypoglycemia were presumed to have been caused by a plasma glucose concentration <70 mg/dl), and asymptomatic hypoglycemia (no typical symptoms of hypoglycemia but the plasma glucose concentration was <70 mg/dl)[6].

Covariates

Demographic and covariate data were extracted from the dEMR. Variables included race, sex, age at t_0, body mass index (BMI, which was calculated as the median non-pregnant BMI in the dEMR), the closest serum creatinine to t_0, the type and dose of sulfonylurea as well as its duration of use. Additionally, concomitant prescriptions for other oral antidiabetic agents occurring during the study period were recorded.

Variant selection and genotyping

The major metabolic pathway for sulfonylurea drug metabolism is through *CYP2C9*, and there is strong evidence for genetic effects on sulfonylurea pharmacokinetics. We selected *CYP2C9*2* and *CPY2C9*3* variants because they affect efficiency of the CYP2C9 enzyme and in turn, substrate clearance[9]. Additionally, we examined 14 variants in eight genes previously associated with sulfonylurea response or insulin release, including: *ABCC8* and *KCNJ11* (regulation of insulin release)[23], *TCF7L2* (sulfonylurea failure)[8], *NOS1AP* (sulfonylurea efficacy)[8], *IRS1, CDKAL1*, and *KCNQ1* (sulfonylurea response)[12], and *POR* (masks the effect of the *CYP2C9* reduced-function alleles)[29] (Supplementary Table 4). Genotyping was performed by the Vanderbilt Technologies for Advanced Genomics (VANTAGE) according to standard protocols using the TaqMan (Applied Biosystems, Foster City, CA, USA) and MassArray (Agena Bioscience, San Diego, CA, USA) platforms. The *CYP2C9* variants were genotyped using TaqMan assays, while the remaining 14 variants were genotyped via the MassArray platform.

For quality control, we examined genotyping call rates and calculated Hardy-Weinberg equilibrium (HWE) of genotype distributions separately in the EA and AA populations. Quality control also included inter- and intra-plate replicates of individuals of parent-child relatedness to check for within-family Mendelian inconsistency. Genotype call rates were 99.6% in both the EA and AA populations and did not differ between cases and controls. The *TCR7L2* SNP rs12225372 failed genotyping in the MassArray pool and was not included in the analysis. The threshold for determining statistical significance of the HWE test was $p < 0.05$. All genotypes examined were in HWE in both populations. All HWE calculations were performed using PLINK v1.07.

Power and sample size

Sample size was estimated for the primary analysis, which was the association between the presence of any *CYP2C9* variant allele (i.e., *2 or *3) and risk of hypoglycemia in the EA population. We estimated that approximately one-third of EAs would carry at least one *CYP2C9* *2 or *3 variant allele[30] and that an odds ratio (OR) of 1.5 was clinically important. To detect an OR of 1.5 with 90% power and a type 1 error of 0.05 required 362 cases and 1086 controls.

Statistical Analysis

Demographic characteristics and other covariates are presented as the median and interquartile range (IQR) for continuous variables, and percentages for categorical variables. Variables were compared between cases and controls using a Wilcoxon rank sum or chi square test as appropriate. Using multivariate logistic regression, the main outcome evaluated in the EA population was the rate of hypoglycemia in patients who carried any *CYP2C9* *2 or *3 variant allele compared to those who carried none (*CYP2C9**1/*1). Given that strong evidence exists linking *CYP2C9* genetic variants with sulfonylurea pharmacokinetics, these variants were selected for more detailed analyses, which included: 1) stratifying by category of hypoglycemia, 2) stratifying by type of sulfonylurea, 3) *CYP2C9* variants in combination with *POR* genotypes, and 4) comparing those individuals with either homozygous or compound heterozygous genotypes for *CYP2C9* *2 and *3 to

individuals with the *CYP2C9* *1/*1 genotype. For the genetic association analyses, logistic regression was performed with hypoglycemia as the outcome variable. The minimally adjusted model included *CYP2C9* genotype, age, and sex as the independent variables. The fully adjusted model included the additional independent variables: type of sulfonylurea, dose of sulfonylurea, BMI, creatinine, and concomitant use of other oral hypoglycemic agents. The analysis of other candidate variants previously associated with sulfonylurea response or insulin release was performed assuming an additive genetic model. A Bonferroni correction for multiple testing was applied based on the number of variants analyzed (n=15). The Bonferroni-adjusted threshold for statistical significance was $p < 0.0033$. The same analyses were also performed separately in the AA population. All analyses were performed using Stata 14 (StataCorp LLC, College Station, TX)[31].

Results

Study population

A total of 824 potential cases and 5,243 potential controls met the initial screening criteria for study inclusion. Upon manual review of the potential cases, 467 patients (383 EAs and 84 AAs) met criteria for hypoglycemia and were matched to controls at a ratio of 1:3, resulting in 1,400 controls (1,148 EAs and 252 AAs). Of the 1,867 selected cases and controls, there were 1,738 samples available for genotyping. After genotype data quality control, there were 356 EA cases and 1,039 EA controls and 78 AA cases and 227 AA controls available for analysis (Figure 1). There were no differences in age, sex, or creatinine values between EA cases and controls (Table 1). The EA cases had a slightly lower BMI compared to controls and were more likely to receive glyburide (Table 1). The AA cases and controls did not differ in age, sex, or creatinine values. The AA cases had a slightly lower BMI compared to AA controls (Supplementary Table 5).

Risk of hypoglycemia in CYP2C9 carriers

In the EA population, compared to patients with the *CYP2C9* *1/*1 genotype, the risk of sulfonylurea-related hypoglycemia was not increased for patients carrying *CYP2C9* *2 or *3 variant alleles (OR = 0.80, 95% confidence interval (CI): 0.68 – 1.13, P= 0.30, fully adjusted model) (Table 2A). Similarly, when compared to individuals homozygous for the *CYP2C9* *1 allele, the risk of hypoglycemia was not increased in patients homozygous or compound heterozygous for *CYP2C9* *2 and *3 alleles (OR = 1.11, 95% CI: 0.62 – 1.98, P= 0.73, fully adjusted model) (Table 2B). Additional analyses that included stratification by category of hypoglycemia or sulfonylurea type, yielded results concordant with the main analysis (Table 2B). When patients were stratified by *POR* genotype, risk of hypoglycemia was higher in patients with *CYP2C9* *2 and *3 variants who also carried the *POR* *28/*28 genotype (OR = 4.36, 95% CI: 1.48–12.80, P=0.007, fully adjusted model) (Table 2B) but this did not cross the Bonferroni-adjusted level of significance (P<0.0033).

In AA patients the risk of hypoglycemia was not associated with *CYP2C9* genotypes (Supplementary Tables 6A & 6B) or individual *CYP2C9* alleles (Supplementary Table 7). We observed no association between sulfonylurea-related hypoglycemia and *CYP2C9*

variants when patients were stratified by *POR* genotypes, however, there were too few patients to test within the *POR* *28/*28 genotype.

Exploratory analyses of SNPs affecting sulfonylurea pharmacodynamics

None of the candidate SNPs potentially affecting sulfonylurea pharmacodynamics was significantly associated with the risk of hypoglycemia in EAs in either minimally or fully adjusted models (Table 3). In AAs, rs10494366, a variant in *NOS1AP*, was associated with increased risk of hypoglycemia in T2DM patients taking a sulfonylurea (OR = 1.84, 95% CI: 1.23–2.74, P=0.003, fully adjusted model) (Supplementary Table 7).

Discussion

In a large retrospective case-control study of EA patients with T2DM receiving sulfonylurea therapy in usual clinical care there was no evidence for association between *CYP2C9* reduced function variants and risk of hypoglycemia. Candidate variants previously reported to alter sulfonylurea response or insulin secretion did not affect the risk of sulfonylurea-related hypoglycemia in this EA population.

Studies investigating the effect of *CYP2C9* variants on the risk of sulfonylurea-related hypoglycemia are relatively limited and have yielded inconsistent results. Multiple studies report that *CYP2C9* reduced-function alleles are associated with increased risk of hypoglycemia in T2DM patients taking sulfonylureas[32–34], while other studies detected no evidence of association[35,36]. Additionally, one study found no evidence of association between *CYP2C9* variants and sulfonylurea-related hypoglycemia in their overall study population, but did observe an association in a subgroup of patients age 60 years and older[11]. The lack of replication across studies may be due in part, to differences in study design including the definition of hypoglycemia, age of study population, and type of sulfonylureas included, as well as to a lack of power resulting from small sample size. Furthermore, two recent studies that detected no effect of *CYP2C9* variants alone reported an increased risk of sulfonylurea-related hypoglycemia in patients who carried either *CYP2C9* *2 or *3 variants and were homozygous for the *POR* *1 allele[29,37]. This suggests *POR* genotypes may mask the effect of *CYP2C9* reduced function variants, thus contributing to the inconsistent association of *CYP2C9* variants with sulfonylurea-related hypoglycemia.

In the present study, which included mild to moderate and severe hypoglycemia, we found no association between *CYP2C9* reduced-function alleles and risk of sulfonylurea-related hypoglycemia in EA patients with T2DM. Given the recent reports of a potential gene-gene interaction between *CYP2C9* and *POR*, we performed additional analysis stratifying by *POR* genotypes. Hypoglycemia was more common in patients with *CYP2C9* reduced-function alleles only in individuals with the *POR* *28/*28 genotype. However, after adjusting for multiple testing the difference was not significant. Additionally, the direction of the association is in contrast to that of previous studies that demonstrated increased risk of hypoglycemia in patients with T2DM carrying a *CYP2C9* reduced-function variant in conjunction with the *POR* *1/*1 genotype[29,37]. The *POR**28 allele is a common variant that results in an amino acid substitution (A503V) in the POR protein. Functional characterization of the POR A503V enzyme demonstrated a modest, but significant

reduction in catalytic activity in four assays[38]. However, none of the assays examined catalytic activity with CYP450 enzymes and evidence suggests that the effect of *POR* variation on drug pharmacokinetics and pharmacodynamics will depend on both the CYP450 enzyme and the drug[39].

In an exploratory investigation in AA patients with T2DM, we examined the potential association between the same genetic variants evaluated in EA patients and sulfonylurea-related hypoglycemia. We found no evidence for association between *CYP2C9* reduced function alleles and sulfonylurea-related hypoglycemia in the AA patients. However, we did observe an association between a candidate pharmacodynamics genetic variant and risk of hypoglycemia in the AA patients taking sulfonylureas. The risk of hypoglycemia was significantly increased in AAs carrying the T allele at rs10494366, a variant in the gene encoding nitric oxide synthase 1 adaptor protein (*NOS1AP*). This is consistent with previous studies suggesting that the T allele was associated with greater sensitivity to some antidiabetic drugs, including a sulfonylurea. In an European population-based cohort study of incident sulfonylurea users, Becker et al reported that patients with T2DM that were heterozygous or homozygous for the G allele at rs10494366 in *NOS1AP* required higher doses of glibenclamide to lower blood glucose levels compared with patients with the TT genotype[22]. A recent study in a Chinese population suggested the TT genotype was associated with a greater decline in insulin resistance following 6 months of repaglinide monotherapy despite higher baseline insulin resistance[40].

The data in the AA population are presented as exploratory because we knew the numbers would be small and thus, the analysis would not be well-powered. Compared to EAs, far fewer AAs (~6%) carry a *CYP2C9**2 or *CYP2C9**3 variant allele[30,41]. Thus, a study to detect an effect of these alleles in AAs (OR of 1.5 with 90% power) would require approximately 1900 cases and 1900 controls. Our finding that the rs10494366 T allele in *NOS1AP* may increase risk of hypoglycemia in AA patients with T2DM receiving sulfonylurea therapy should be regarded as hypothesis generating, and further studies in larger, independent cohorts are necessary to validate this finding in the AA population.

There were some limitations to this study. Even though we present the largest study to date assessing the association between *CYP2C9* genotypes and hypoglycemia in EA patients with T2DM taking a sulfonylurea, the numbers of homozygous recessive genotypes for *CYP2C9* *2 and *3 variants were low. The retrospective nature of this study performed in records from usual clinical care introduces inherent limitations. The dEMRs used for the study do not contain details from medical visits to other health care facilities, thus not all information was obtained or recorded for every patient. In the current study, a pre-sulfonylurea HbA1c was only available for approximately half of the patients, and therefore, could not be included as a covariate in the analysis without a significant reduction in sample size and power. However, the records do include a large amount of information collected as part of usual care and thus allowed the study to be performed in a population in whom the findings would be applicable.

It is possible that genetic variants in other *CYP2C* subfamily members could affect risk of sulfonylurea-related hypoglycemia. For example, there is evidence that *CYP2C19* may

contribute to the metabolism of the sulfonylurea gliclazide[42], and multiple common variants affecting function of the CYP2C19 enzyme have been reported[43,44]. Thus, we cannot exclude an effect of variants other than those we evaluated.

In conclusion, in a large study of patients receiving sulfonylurea therapy for treatment of T2DM, we found no clinically important predictors of hypoglycemia among genes associated with sulfonylurea pharmacokinetics or pharmacodynamics. These results suggest that presently, there is not sufficient evidence that preemptive genotyping of these variants will be clinically useful for reducing the risk of hypoglycemia in patients with T2DM receiving sulfonylurea therapy. Evidence suggests it is possible that there are subgroups of patients in which multiple genetic variants affect risk for sulfonylurea-related hypoglycemia. Further studies are needed to determine the clinical utility of these genetic variants in these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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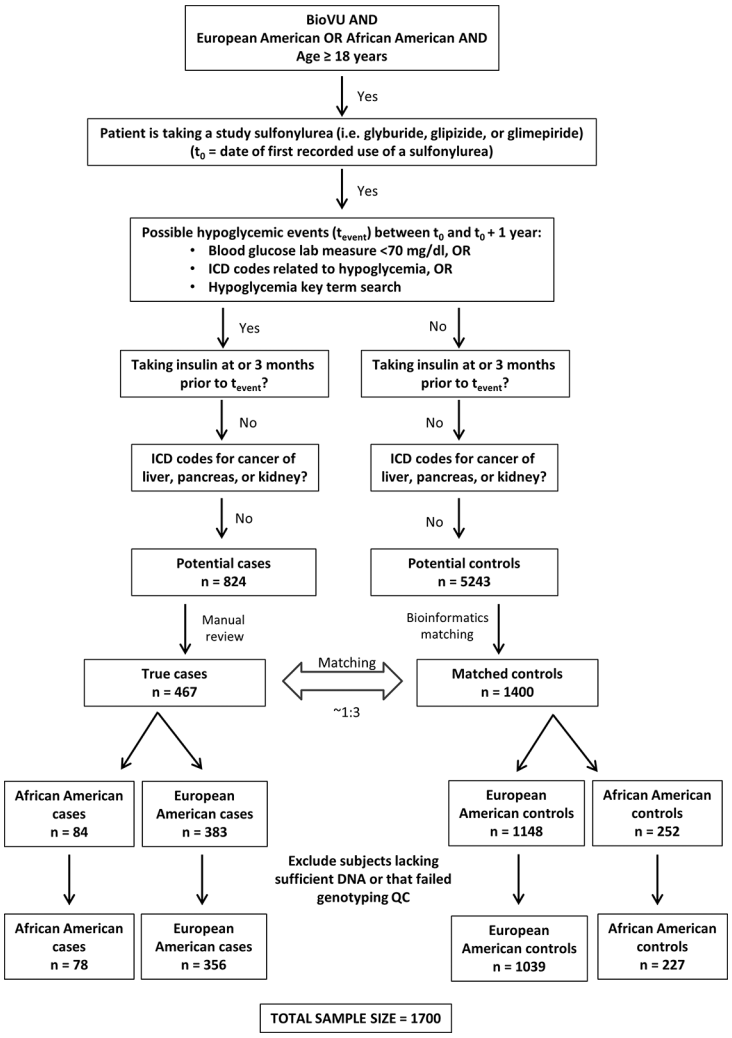

Figure 1: Flow diagram of case and control identification

A bioinformatics algorithm was used in the deidentified electronic medical record to identify cases and controls available in BioVU, the Vanderbilt University Medical Center DNA repository.

Table 1:

Characteristics of European American study population

Characteristic	Cases (n=356)	Controls (n=1039)	p-value
Female, n (%)	182 (51.1)	525 (50.5)	0.85
Age at t_0, years	60.8 (53.3 – 67.9)	60.7 (52.9 – 68.1)	0.89
BMI, kg/m^2	31.0 (27.1 – 35.9)	32.1 (28.1 – 37.1)	**0.004**
Creatinine, mg/dL	0.9 (0.8 – 1.2)	1.0 (0.8 – 1.2)	0.92
Sulfonylurea, n (%)			**0.014**
Glimepiride	117 (32.9)	35.2)	
Glipizide	101 (28.4)	34.2)	
Glyburide	138 (38.8)	318 (30.6)	
Sulfonylurea dose, mg			
Glimepiride	2.0 (1.0 – 4.0)	2.0 (2.0 – 4.0)	0.21
Glipizide	5.0 (5.0 – 10.0)	5.0 (5.0 – 10.0)	0.94
Glyburide	5.0 (2.5 – 5)	5.0 (2.5 – 5.0)	0.65
Concomitant oral antidiabetic drug use, n (%)	249 (69.9)	764 (73.5)	0.21
Category of hypoglycemia, n (%)		N/A	N/A
Asymptomatic	239 (67.1)		
Probable	68 (19.1)		
Documented	43 (12.1)		
Severe	6 (1.7)		

Data shown are median (interquartile range) and percentage (counts) for continuous and categorical data, respectively. Wilcoxon rank sum and Chi square tests were used to compare groups as appropriate. Missing data for the following variables: Body mass index (BMI): 7 cases, 18 controls; creatinine: 2 cases, 4 controls; glimepiride dose: 11 controls; glipizide dose: 3 controls; glyburide dose: 9 controls

Table 2A:

CYP2C9 genotypes and sulfonylurea-related hypoglycemia in European American patients

***CYP2C9* genotype**	**Frequency of genotypes**		**Minimally adjustedmodel**		**Fully adjusted model**	
	Cases (n=356)	**Controls (n=1039)**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
*1/*1	224 (62.9%)	627 (60.3%)	Reference			
*1/*2, *1/*3, *2/*2, *2/*3, or *3/*3	132 (37.1%)	412 (39.7%)	0.90 (0.70 – 1.15)	0.40	0.80 (0.68–1.13)	0.30

Logistic regression analysis was performed assuming a dominant model.

The minimally adjusted model included *CYP2C9* genotype, age, and sex as covariates

The fully adjusted model included *CYP2C9* genotype, age, sex, type of sulfonylurea, dose of sulfonylurea, BMI, creatinine, and concomitant use of other oral antidiabetics.

OR (95% CI) = odds ratio (95% confidence interval)

Table 2B:

Additional analyses of *CYP2C9* genotypes and sulfonylurea-related hypoglycemia in European American patients

Type of Analysis	Minimally adjusted				Fully adjusted			
	*1/*1[1]	*1/*2, *1/*3, *2/*2, *2/*3, or *3/*3[1]	OR (95% CI)	p-value	*1/*1[1]	*1/*2, *1/*3, *2/*2, *2/*3, or *3/*3[1]	OR (95% CI)	p-value
By Severity of Hypoglycemia								
Asymptomatic	142/769(18.5)	97/509 (19.1)	1.05 (0.79, 1.40)	0.74	136/731 (18.6)	95/495 (19.2)	1.02 (0.78, 1.37)	0.90
Probable	47/674 (7.0)	21/433 (4.8)	0.67 (0.40, 1.14)	0.67	46/641 (7.2)	21/421 (5.0)	0.67 (0.40, 1.15)	0.15
Documented	30/657 (4.6)	13/425 (3.1)	0.66 (0.34, 1.28)	0.22	30/625 (4.8)	13/413 (3.1)	0.64 (0.33, 1.25)	0.20
Severe	5/632 (0.8)	1/413 (0.2)	0.30 (0.04, 2.63)	0.28	5/300 (0.8)	1/401 (0.2)	0.29 (0.03, 2.59)	0.27
Stratified by type of sulfonylurea								
Glimepiride	77/297 (25.9)	40/186 (21.5)	0.77 (0.50, 1.20)	0.25	75/281 (26.7)	40/180 (22.2)	0.78 (0.50, 1.22)	0.27
Glyburide	61/278 (21.9)	40/178 (22.5)	1.04 (0.66, 1.63)	0.88	61/276 (22.1)	40/176 (22.7)	1.05 (0.66, 1.66)	0.84
Glipizide	86/276 (31.2)	52/180(28.9)	0.89 (0.59, 1.35)	0.59	81/255 (31.8)	50/174 (28.7)	0.84 (0.55, 1.30)	0.44
Stratified by POR genotype:								
*1/*1	121/443 (27.3)	70/291 (24.1)	0.83 (0.59, 1.17)	0.30	118/428 (27.6)	69/280 (24.6)	0.85 (0.60, 1.21)	0.37
*1/*28	91/346 (26.3)	47/217 (21.7)	0.77 (0.52, 1.15)	0.21	88/325 (27.1)	46/215 (21.4)	0.72 (0.47, 1.09)	0.12
*28/*28	12/62 (19.4)	15/36 (41.7)	3.01 (1.20, 7.53)	0.019	11/59 (18.6)	15/35 (42.9)	4.36 (1.48, 12.80)	0.007
Type of Analysis	**Minimally adjusted**				**Fully adjusted**			
	***1/*1[1]**	***2/*2, *2/*3, or *3/*3[a]**	**OR (95% CI)**	**p-value**	***1/*1[1]**	***2/*2, *2/*3, or *3/*3[1]**	**OR (95% CI)**	**p-value**
Wild type vs compound heterozygous or homozygous	224/851 (26.3)	18/59 (30.5)	1.22 (0.68, 2.16)	0.51	217/812 (26.7)	18/59 (30.5)	1.11 (0.62 – 1.98)	0.73

All logistic regression analyses were performed assuming a dominant model. OR (95%CI): odds ratio (95% confidence interval); P: P-value

Minimally adjusted model: include sex and age as covariates.

Fully adjusted model: include age, sex, type of sulfonylurea, dose of sulfonylurea, BMI, creatinine, and concomitant use of other oral antidiabetics

[1]The cells represent the number of cases with the genotype / number of cases and controls with the genotype per category. The category is defined by the row variable.

Table 3:

Association between candidate variants and sulfonylurea-related hypoglycemia in European American patients

SNP	Gene	Minimally Adjusted Model		Fully Adjusted Model	
		OR (95% CI)	p-value	OR (95% CI)	p-value
rs1799853 (*2)	*CYP2C9*	0.90 (0.71 – 1.15)	0.41	0.88 (0.69 – 1.14)	0.33
rs1057910 (*3)	*CYP2C9*	1.10 (0.77–1.56)	0.60	1.05 (0.73 – 1.50)	0.79
rs757110	*ABCC8* (*SUR1*)	0.90 (0.76 – 1.08)	0.25	0.93 (0.78 – 1.11)	0.43
rs1799854	*ABCC8* (*SUR1*)	1.07 (0.90 – 1.27)	0.48	1.04 (0.87 – 1.24)	0.68
rs1799859	*ABCC8* (*SUR1*)	1.14 (0.95 – 1.38)	0.17	1.15 (0.94 – 1.40)	0.17
rs5219	*KCNJ11*	0.92 (0.77 – 1.09)	0.32	0.94 (0.79 – 1.13)	0.51
rs7903146	*TCF7L2*	0.98 (0.82 – 1.18)	0.85	0.96 (0.80 – 1.15)	0.65
rs10494366	*NOS1AP*	1.07 (0.90 – 1.28)	0.45	1.06 (0.89 – 1.27)	0.52
rs1801278	*IRS1*	0.96 (0.68 – 1.34)	0.82	0.98 (0.71 – 1.40)	0.98
rs2943641	*IRS1*	1.04 (0.87 – 1.24)	0.70	0.97 (0.80 – 1.16)	0.71
rs7756992	*CDKAL1*	1.06 (0.88 – 1.28)	0.52	1.08 (0.89 – 1.30)	0.46
rs163184	*KCNQ1*	0.99 (0.84 – 1.17)	0.90	0.96 (0.81 – 1.13)	0.61
rs2237892	*KCNQ1*	0.91 (0.63 – 1.32)	0.62	0.90 (0.62 – 1.30)	0.56
rs2237895	*KCNQ1*	0.96 (0.81 – 1.14)	0.64	0.93 (0.77 – 1.11)	0.41
rs1057868 (*28)	*POR*	0.98 (0.81 – 1.19)	0.87	0.96 (0.79 – 1.17)	0.68

Logistic regression analyses were performed assuming an additive model to test for association between individual genetic variants and sulfonylurea-induced hypoglycemia.

Minimally adjusted models included *CYP2C9* genotype, age, and sex.

Fully adjusted models included *CYP2C9* genotype, age, sex, type of sulfonylurea, dose of sulfonylurea, BMI, creatinine, and concomitant use of other oral antidiabetics.

OR (95% CI) = odds ratio (95% confidence interval)