Role of Common Sequence Variants in Insulin Secretion in Familial Type 2 Diabetic Kindreds

The sulfonylurea receptor, glucokinase, and hepatocyte nuclear factor 1α genes

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OBJECTIVE — We have demonstrated high heritability of insulin secretion measured as acute insulin response to glucose times insulin sensitivity (disposition index). Furthermore, we showed that obese normoglycemic family members of a type 2 diabetic proband failed to compensate for the insulin resistance of obesity by increasing insulin secretion. In this study, we tested the primary hypotheses that previously described variants in the pancreatic sulfonylurea receptor gene (SUR1 or ABCC8), glucokinase (GCK) gene, or hepatocyte nuclear factor 1α (TCF1 or HNF1α) gene contribute to the inherited deficiencies of insulin secretion and β-cell compensation to insulin resistance, as well as the secondary hypotheses that these variants altered insulin sensitivity.

RESEARCH DESIGN AND METHODS — We typed 124 nondiabetic members of 26 familial type 2 diabetic kindreds who had undergone tolbutamide-modified intravenous glucose tolerance tests for two variants of the ABCC8 (sulfonylurea) gene, two variants of the GCK gene, and one common amino acid variant in the TCF1 (HNF1α) gene. All family members were classified as normal or having impaired glucose tolerance based on oral glucose tolerance testing. We used minimal model analysis to calculate the insulin sensitivity index (S_I) and glucose effectiveness (S_G), and acute insulin response to glucose was calculated as the mean insulin excursion above baseline during the first 10 min after the glucose bolus. Disposition index (DI), a measure of β-cell compensation for insulin sensitivity, was calculated as insulin sensitivity times acute insulin response. Effects of polymorphisms were determined using mixed effects models that incorporated family membership and by a likelihood analysis that accounted for family structure through polygenic inheritance.

RESULTS — An intronic variant of the ABCC8 gene just upstream of exon 16 was a significant determinant of both DI and an analogous index based on acute insulin response to tolbutamide. Surprisingly, heterozygous individuals showed the lowest indexes, whereas the DI in the two homozygous states did not differ significantly. Neither the exon 18 variant nor the variants in the GCK and TCF1 genes were significant in this model. However, combined genotypes of ABCC8 exon 16 and 18 variants again significantly predicted both indexes of glucose and tolbutamide-stimulated insulin secretion. Unexpectedly, a variant in the 3′ untranslated region of the GCK gene interacted significantly with BMI to predict insulin sensitivity.

CONCLUSIONS — The exon 16 variant of the ABCC8 gene reduced β-cell compensation to the decreased insulin sensitivity in the heterozygous state. This may explain the observation from several groups of an association of the ABCC8 variants in diabetes and is consistent with other studies showing a role of ABCC8 variants in pancreatic β-cell function. However, our study focused on individuals from relatively few families. Ascertainment bias, family structure, and other interacting genes might have influenced our unexpected result. Additional studies are needed to replicate our observed deficit in β-cell compensation in individuals heterozygous for ABCC8 variants. Likewise, the role of the GCK 3′ variant in the reduced insulin sensitivity of obesity will require further study.

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Type 2 diabetes is characterized by a strong genetic predisposition. Ongoing studies from our laboratory and others have suggested multiple possible susceptibility loci (1–4). These studies will eventually identify genes important to the pathogenesis of type 2 diabetes, but heterogeneity, epistasis, and gene-environment interactions are probable and will complicate a full understanding of diabetes pathogenesis. To understand these complex interactions, we, in addition to other studies, have taken a complementary approach to examine the genetic determinants of the prediabetic traits in normoglycemic individuals at risk for the development of diabetes. In support of this approach, both diminished insulin sensitivity and insulin secretion have been shown to precede and predict type 2 diabetes (5,6). Furthermore, insulin sensitivity is familial and segregates as an autosomal trait (7–9). Recently, Sakul et al. (10) showed that first-phase insulin secretion was also familial in Pima Indians, and we demonstrated

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Abbreviations: $AIR_{glucose}$, acute insulin response to glucose; $AIR_{tolbutamide}$, acute insulin response to tolbutamide; DI, disposition index; DIT, disposition index of tolbutamide; GCK, glucokinase; S_G, glucose effectiveness; S_I, insulin sensitivity index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

high heritability of an index of β-cell compensation for insulin resistance—the disposition index (DI) (1). These studies suggest that common genetic variants may influence measures of insulin sensitivity, insulin resistance, and β-cell compensation among nondiabetic family members at risk for type 2 diabetes. The effect of these genes may be difficult to detect in traditional linkage studies of type 2 diabetes.

Association studies have potentially more power than linkage studies to detect more modest genetic determinants (11) but when conducted on a population may be subject to spurious association due to population stratification (12). By conducting the association study using certain family structures, this potential error may be avoided (13). The application of this approach to quantitative (continuous) traits thus allows for the evaluation of the effects of common genetic variants in families. These genetic variants may either influence the trait directly or alternatively may be associated (in linkage disequilibrium) with an as yet undetected variant.

Several previously reported genetic variants may either directly alter the ability of the pancreatic β-cell to respond to decreased insulin sensitivity or be in linkage disequilibrium with functional variants that alter gene function. Inoue et al. (14) initially demonstrated an association of two variants in the pancreatic sulfonylurea receptor gene (SUR1, now called ABCC8) with type 2 diabetes. One variant (exon 18) was silent (Thr759Thr) and the other intronic (exon 16 −3C → −3T). Subsequent studies have confirmed the association of these polymorphisms with type 2 diabetes (15–17) and morbid obesity (17), although both the specific allele and associated polymorphism have varied among studies. Hansen et al. (16) suggested a specific combined genotype-reduced insulin secretion in 10 healthy Caucasians. Goksel et al. (18) described a silent variant in exon 31 that raised fasting and postchallenge insulin levels in nondiabetic Hispanic patients. Reduced second-phase insulin response was seen in both normoglycemic individuals and those with impaired glucose tolerance carrying the exon 16 −3T allele (19).

Coding variants of the glucokinase (GCK) gene are an important cause of decreased glucose-stimulated insulin secretion and maturity-onset diabetes of the young (20), but are uncommon in typical type 2 diabetes (21). A common variant at position −30 of the GCK promoter decreased the 30-min insulin response to oral glucose in middle-aged Japanese-American men (22). We reported previously that a single nucleotide insertion in the 3′ untranslated region of the GCK gene segregated with diabetes in one family but did not alter fasting glucose (23). Mutations of the hepatocyte nuclear factor 1α gene (HNF1α or TCF1) are also an important cause of insulin secretion defects causing early-onset autosomal-dominant diabetes (24). A number of common amino acid variants in the TCF1 gene do not segregate with diabetes. In contrast, Urhammer et al. (25) reported that the Ala98Val variant resulted in decreased 30-min insulin response to oral glucose.

Based on the evidence that insulin secretion and insulin sensitivity are heritable traits, and the prior evidence that these common variants may alter insulin secretion and diabetes risk in population studies, we tested the hypothesis that these three genes contributed to the inherited insulin secretion defect in familial type 2 diabetes. We show that the exon 16 variant of the ABCC8 gene influences the two indexes of β-cell compensation. In contrast, we could not demonstrate a role for GCK or TCF1 in the inherited control over β-cell compensation.

Table 1—*Characteristics of the study population*

n	124
Sex	53 male, 71 female
Diagnosis	98 normal glucose tolerance, 26 impaired glucose tolerance
Fasting glucose (mmol/l)	5.12 ± 0.58
Fasting insulin (pmol/l)	36.9 (32.2–42.2)
S_G	0.0174 (0.0160–0.0188)
S_I ($\times 10^{-5}$ min^{-1}/[pmol/l])	6.85 (5.84–8.03)
$AIR_{glucose}$ (pmol/l)	179 (158–203)
S_I*$AIR_{glucose}$	0.0115 (0.0093–0.0143)
$AIR_{tolbutamide}$ (pmol/l)	346 (303–394)
S_I*$AIR_{tolbutamide}$	0.0237 (0.0213–0.0263)

Characteristics of the full study population are shown. Skewed terms are means (95% CI); normal terms are means ± SD.

RESEARCH DESIGN AND METHODS

Subjects

We studied 124 individuals who had normal fasting glucose levels and had normal or impaired glucose tolerance by World Health Organization criteria on 75-g oral glucose tolerance tests. All individuals were members of families selected for having at least two siblings with type 2 diabetes with onset before age 65 years (1) and had undergone tolbutamide-modified intravenous glucose tolerance tests as described elsewhere (1,26). All studies were performed on the General Clinical Research Center of the University of Utah. All subjects gave informed con-

Table 2—*Marginal means and genotype distributions for ABCC8 (SUR1) exon 18 (Thr759)*

Genotype	1/1 (C/C)	1/2 (C/T)	2/2 (T/T)	*P*
n	100	19	1	
S_G	0.0161 (0.0141–0.0183)	0.0168 (0.0123–0.0229)	—	0.825
S_I (10^5)	5.84 (4.71–7.25)	5.32 (3.20–8.85)	—	0.75
$AIR_{glucose}$	166.7 (139.8–198.9)	200.5 (132.8–302.8)	—	0.482
DI	0.846 (0.62–1.15)	0.955 (0.459–1.98)	—	0.669
DIT	0.212 (0.18–0.25)	0.218 (0.148–0.322)	—	0.552

Table 2 shows the means by genotype after correction for covariates age and BMI. Data are geometric means (95% CI). All variables were ln-transformed before analysis using a mixed effects model. *P* values are reported using the mixed effects model described in RESEARCH DESIGN AND METHODS and carrier status except for the ABCC8 exon 16 variant. Values reflect only main effects and the interaction of genotype with family membership. Units are as follows: S_I ($\times 10^{-5}$ min^{-1}/[pmol/l]); $AIR_{glucose}$, pmol/l. Other variables from Table 1 were not tested in this analysis.

sent according to a protocol approved by the Institutional Review Board.

The individuals studied were drawn from 57 sibships and 26 extended families. Both sibling and extended relative relationships were present in many families. We studied a mean of 4.8 individuals/family (range 1–11). Of the simple sibships within these families, 20 comprised a single individual, 18 sibships included two siblings, 14 sibships included three siblings, and seven sibships included four or five siblings. Eleven of the 26 families included sibships from more than one generation. Although a small number of spouses were studied, they were not included in the mixed-effects models described below.

Genotypic analysis

Variants for ABCC8 (SUR1) (14), the −30 GCK promoter variant (27), and TCF1 (HNF1α) codon 98 were detected as described elsewhere (28) using restriction enzymatic digestion of the appropriate enzymatic amplification product and agarose electrophoresis. The GCK 3′ untranslated variant (exon 10) was detected by heteroduplex mismatch analysis after labeling with the enzymatic amplification product with [α-^{32}P]dCTP (23) and separation on 1X Mutation Detection Enhancement gels (FMC Bioproducts, Rockland, ME).

Statistical analysis

Insulin sensitivity index (S_I) and glucose effectiveness (S_G) were calculated from the minimal model (29). Acute insulin response to glucose was estimated as the mean insulin response above baseline from 2 to 10 min after glucose infusion. To determine the effects of the ABCC8 variant on sulfonylurea-induced insulin secretion, we also calculated the acute insulin response to tolbutamide ($AIR_{tolbutamide}$) as the mean insulin from 22 to 30 min. For analysis, we examined the product of these acute insulin responses with the S_I. Because individuals homozygous for the minor allele were rare, we conducted most analyses on carrier status and thus grouped heterozygous individuals with individuals homozygous for the minor allele. For ABCC8 exon 16, we examined genotype rather than carrier status. BMI, S_I, DI (S_I*$AIR_{glucose}$), and DI tolbutamide (DIT; S_I*$AIR_{tolbutamide}$) were each log-transformed to normality.

We tested for an effect of each gene variant on DI (S_I*$AIR_{glucose}$), S_I*$AIR_{tolbutamide}$, S_I, and S_G, although the primary goal of the analysis was to test β-cell compensation (DI and DIT). Our primary analysis used mixed-effects models similar to those proposed by Allison et al. (13), except that we coded all sibships within a family under a single family number. Our ability to reject apparent association in the presence of population admixture using this more complicated family structure is uncertain. For mixed effects models, we included age and ln(BMI) as covariates, pedigree membership (coded as a numeric family identifier) as a random factor, and sex, diagnosis (normal glucose tolerance or impaired glucose tolerance), and genotype (carrier status) as fixed factors. We report all results with the inclusion of an interaction term for genotype by family number; otherwise only main effects were modeled in the primary analyses (13). Interactions of each variant with ln(BMI) and age were tested only as secondary analyses. The inclusion of the genotype by family interaction terms altered significance of genotype on some dependent variables, as noted below. Analyses were conducted in SPSS for Windows (SPSS, Chicago). Significance values are reported without Bonferroni correction.

Because the mixed effects model has been validated only for simple sibships, we also used a likelihood method to test for association while accounting for family structure through polygenic inheritance. This model compares the likelihood of the data with the genetic variant to the likelihood without the marker (null hypothesis). The likelihood ratio statistic is distributed as an χ^2 with the number of degrees of freedom equal to one less than the number of genotypes. We used the Pedigree Analysis Package (30) to conduct these analyses. All skewed data were ln-transformed before analysis. The likelihood analyses do not allow for interactions between genotype and continuous covariates.

Table 3—*Marginal means and genotype distribution for ABCC8 (SUR1) exon 16 (–3 C/T) variant*

Genotype	1/1 (C/C)	1/2 (C/T)	2/2 (T/T)	*P*
n	49	53	20	
S_G	0.0174 (0.0149–0.0202)	0.0179 (0.0127–0.0175)	0.0173 (0.0133–0.0225)	0.254
S_I (10^5)	6.85 (5.36–8.74)	4.73 (3.66–6.12)	6.75 (4.43–10.28)	0.061
$AIR_{glucose}$	172.3 (140.8–210.9)	161.8 (130.4–200.8)	208.2 (147.2–294.4)	0.384
DI	1.094 (0.778–1.54)	0.604 (0.422–0.865)	1.39 (0.77–2.50)	0.001
DIT	0.244 (0.203–0.293)	0.177 (0.146–0.0214)	0.261 (0.190–0.357)	0.027

Data are geometric means (95% CI). For methods, see Table 2.

RESULTS — The characteristics of the study population are summarized in Table 1. Tables 2–6 show the distribution of alleles for each variant and the impact of each variant tested for each of the traits, shown as marginal means after correction for age and BMI as covariates but not family membership. We initially used the mixed effects model to test the hypothesis that each variant predicted DI, S_I, S_G, $AIR_{glucose}$, or S_I*$AIR_{tolbutamide}$. In this analysis, diagnosis (normoglycemic vs. IGT; $P = 0.003$), age ($P = 0.03$), BMI ($P = 0.03$), and family membership ($P = 0.026$) were all significant determinants of DI. The intronic variant at position −3

Table 4—*Marginal means and genotype distributions for GCK promoter variant*

Genotype	1/1 (G/G)	1/2 (G/A)	2/2 (A/A)	*P*
n	87	32	2	
S_G	0.0167 (0.0144–0.019)	0.0159 (0.0129–0.0195)	0.0120 (0.006–0.0244)	0.263
S_I (10^5)	6.24 (5.00–7.80)	4.72 (3.38–6.58)	7.08 (2.25–22.8)	0.079
$AIR_{glucose}$	162.7 (135.9–194.7)	207.7 (159.4–270.6)	83.7 (33.7–207.9)	0.462
DI	0.857 (0.62–1.186)	0.913 (0.562–1.482)	0.680 (0.123–3.61)	0.648
DIT	0.218 (0.183–0.259)	0.206 (0.159–0.266)	0.217 (0.089–0.533)	0.294

Data are geometric means (95% CI) . For methods, see Table 2.

Table 5—*Marginal means and genotype distributions for GCK 3′ untranslated variant*

Genotype	1/1	1/2	2/2	*P*
n	75	45	3	
S_G	0.0156 (0.0135–0.0181)	0.0180 (0.0148–0.0218)	0.0109 (0.005–0.0229)	0.844
S_I (10^5)	6.0 (4.70–7.66)	5.22 (3.78–7.22)	9.26 (2.70–31.8)	0.55
$AIR_{glucose}$	187.4 (154–228)	155.4 (120.0–201.1)	75.5 (28.3–201.6)	0.227
DI	0.949 (0.672–1.342)	0.754 (0.476–1.194)	0.46 (0.08–2.63)	0.324
DIT	0.228 (0.190–0.275)	0.193 (0.151–0.247)	0.167 (0.067–0.428)	0.244

Data are geometric means (95% CI). For methods, see Table 2.

in ABCC8 exon 16 was a significant determinant of both DI ($P = 0.001$) and S_I*$AIR_{tolbutamide}$ ($P = 0.027$). We found a marginal effect of the exon 16 variant on S_I ($P = 0.061$) when genotype by family interaction was included, which reached $P = 0.047$ without the interaction term. In contrast, we found no effect of the exon 18 Thr759 variant. Neither ABCC8 exon 16 nor exon 18 variants determined $AIR_{glucose}$ or S_G, and no interaction with BMI was observed ($P > 0.5$). Using the alternative likelihood analysis that compares two models, one with and the other without the variant of interest, we again found a significant association of the exon 16 variant with DI ($\chi^2 = 6.62$; $P = 0.035$) but not with $AIR_{glucose}$ or S_I ($\chi^2 = 5.06$; $P = 0.079$). The exon 18 variant showed no associations with any trait by this method.

Previous studies (14–16) suggested that some ABCC8 haplotypes represented a higher diabetes risk than others. To examine this hypothesis among family members, we performed a joint analysis of all five haplotypes shown in Table 7 using the mixed effects models. As with the exon 16 −3 C/T variant alone, joint ABCC8 haplotypes significantly predicted both the DI ($P = 0.037$) and the analogous tolbutamide index (S_I*$AIR_{tolbutamide}$; $P = 0.030$). However, inspection of marginal means (Table 3) shows a 50% reduction in DI for exon 16 C/T heterozygotes regardless of exon 18 genotype; this was confirmed in post hoc analyses, and suggested that exon 18 made little or no contribution to DI in this population. In contrast, exon 18 did appear to contribute to S_I*$AIR_{tolbutamide}$ based on post hoc.

Using mixed effects models, neither the GCK −30 promoter nor the exon 10 3′ untranslated variant influenced either index of insulin secretion ($P > 0.2$ for all analyses). Furthermore, as anticipated, the −30 promoter variant had no effect on either S_G or S_I. Unexpectedly, however, the 3′ untranslated region variant interacted significantly with BMI to predict S_I ($P = 0.003$) but not measures of insulin secretion. No variant showed a significant association using the alternative likelihood analysis, in which interaction effects were not modeled.

Analysis of the TCF1 (HNF1α) Ala98Val variant was limited by the small number of carriers. No effect was found on either measure of insulin secretion, but in a model without interactions (except genotype by family number; see RESEARCH DESIGN AND METHODS), Ala98Val significantly predicted both S_I ($P = 0.009$) and S_G ($P = 0.043$). These effects were not replicated using the likelihood analysis and may represent type 1 errors.

Table 6—*Marginal means and genotype distributions for TCF1 (HNF1α) Ala98Val*

Genotype	1/1 (A/A)	1/2 (A/V)	2/2 (V/V)	*P*
n	119	5	0	
S_G	0.0166 (0.0146–0.0187)	0.0146 (0.008–0.0218)	—	0.38
S_I (10^5)	5.99 (4.88–7.34)	3.15 (1.37–7.26)	—	0.009
$AIR_{glucose}$	173 (147–206)	161 (81–318)	—	0.753
DI	0.90 (0.68–1.21)	0.42 (0.13–1.35)	—	0.105
DIT	0.22 (0.19–0.26)	0.16 (0.09–0.30)	—	0.418

Data are geometric means (95% CI). For methods, see Table 2.

CONCLUSIONS — Several studies have demonstrated an association of ABCC8 (SUR1) variants with type 2 diabetes (14–17). Despite linkage disequilibrium between the variants, most studies found an association of either the exon 16 (intronic) variant (14,15) or the silent exon 18 variant (14,16,17) but not both. Furthermore, the allele associated with diabetes has been inconsistent (15). No functional variant in the ABCC8 gene or in the adjacent KCNJ11 (KIR 6.2) subunit (14,17,31,32) has been identified to explain this association. Hansen et al. (16) reported that 10 healthy Danish Caucasians who were heterozygous at both ABCC8 variants had reduced insulin response to tolbutamide. Reduced second-phase insulin secretion was reported in both normoglycemic and individuals with impaired glucose tolerance who carried either one or two copies of the exon 16 −3T variant (19).

In our study, individuals heterozygous for the exon 16 variant had reduced insulin secretion in response to both glucose and tolbutamide relative to individuals homozygous for either allele. Because we did a large number of tests, the significance level of our findings is relatively modest; and because that significance lies entirely with individuals heterozygous for the variant, our results may represent a type 1 error. Additionally, much of the evidence in our study comes from relatively few families. Nonetheless, a biological effect seen predominately in individuals heterozygous for a variant does have precedent. In addition to the report of Hansen et al. (16), heterozygosity of the HLA D-region genes is well known to represent the highest risk for type 1 diabetes (33). Furthermore, Horikawa et al. (34) recently reported that heterozygosity for certain haplotpes at the Calpain 10 gene resulted in the highest risk for type 2 diabetes among a Hispanic population. Given the considerable prior data supporting a role for ABCC8 in diabetes risk and insulin secretion and the lack of known functional coding variants in this gene, these intronic variants may directly alter gene function. Alternatively, additional undiscovered variants, particularly variants in other introns that are in linkage disequilibrium with the exon 16 and 18 variants, may in fact be the actual cause of the observed physiological abnormality. An additional synonymous variant in exon 31

reduced fasting and 2-h insulin levels in Hispanic subjects (18) and was not typed in the present study nor in most other reported studies. Among possible biological explanations for the decreased insulin secretion in heterozygous individuals are interactions among gene products of the two alleles in the assembly of the potassium channel, or interaction through altered tissue specific gene expression for the two alleles. Our studies extend the earlier findings and suggest that common ABCC8 variants contribute to the polygenic inheritance of DI, but the means by which ABCC8 variants alter insulin secretion and diabetes risk will require additional study.

Although insulin response to oral glucose was reduced in Japanese men who carried the GCK −30 G → A variant, recent oral and intravenous glucose tolerance test studies failed to find an effect in unrelated Finnish (35) or Danish (36) Caucasians. We likewise find no role for this variant in determining DI. We were also unable to demonstrate an effect of the 3′ untranslated region variant on DI, but this variant interacted with obesity (BMI) to influence S_I. Because this finding was unexpected and not a prior hypothesis, and we did not do a Bonferroni correction, these findings may be spurious. Confirmatory studies will be required, but the effect is biologically plausible. Glucokinase is expressed in the liver, and this variant might alter hepatic insulin sensitivity, which in turn might be reflected in the minimal model determination of S_I. A role for either GCK variant in homozygous individuals remains possible and would have been difficult to detect in the present study because of the small number of individuals homozygous for the variant.

Two studies of Urhammer et al. (25, 28) suggested a role for the Ala98Val variant of TCF1 (HNF1α) in insulin response to oral glucose, but they did not find a response to intravenous glucose. Our results confirm the lack of effect on indexes of insulin secretion derived from intravenous glucose in the context of a strong family history of type 2 diabetes. However, we again found an unexpected effect of this variant on both S_I and S_G. These effects were not seen by Urhammer et al. (28), and because the number of carriers in our study was small and these were not prior hypotheses, these findings also may be spurious. Like GCK, TCF1 is expressed in the liver, and effects on hepatic insulin sensitivity are possible. However, individuals with *MODY3* resulting from variants of TCF1 have defects primarily in insulin secretion without reduced insulin sensitivity (37). Because this variant is unusual, further testing of this hypothesis will require a sizable population that has been assessed for insulin sensitivity.

Table 7—*Combined haplotype analysis for ABCC8*

Genotype	*n*	Exon 16 −3 C/T	Exon 18 Thr759Thr	S_I*$AIR_{glucose}$	S_I*$AIR_{tolbutamide}$
1	35	C/C	C/C	0.096 (0.061–0.152)	0.023 (0.019–0.028)
2	12	C/C	C/T	0.098 (0.044–0.220)	0.029 (0.020–0.040)
3	45	C/T	C/C	0.057 (0.034–0.097)	0.019 (0.015–0.024)
4	7	C/T	C/T	0.056 (0.021–0.145)	0.012 (0.008–0.018)
5	20	T/T	C/C	0.134 (0.065–0.277)	0.027 (0.020–0.036)

Estimated means (95% CIs) are given from the mixed effects model, adjusted for covariates, and transformed back to linear scale. In pairwise comparisons, S_I*$AIR_{glucose}$ (DI) was significantly different for genotype 3 vs. genotype 5; S_I*$AIR_{tolbutamide}$ (DIT) was significantly different for genotypes 1 vs. 4, 2 vs. 3, 2 vs. 4, 3 vs. 4, 3 vs. 5, and 4 vs. 5 (all <0.05).

In conclusion, our data support an effect of ABCC8 (SUR1) variants on β-cell compensation to insulin sensitivity, measured either as acute insulin response to glucose or tolbutamide. A similar effect is observed when haplotypes comprising both exon 16 and exon 18 variants are examined. The surprising finding that this effect is strongest in heterozygous individuals will require confirmation and further study. Although ABCC8 does not act as a major gene for type 2 diabetes (38), the present study and those of others (16,18,19) suggest that ABCC8 variants contribute to the observed familiality of DI (1) in familial type 2 diabetic kindreds.

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