The Impact of Genetic Variation in the *G6PC2* Gene on Insulin Secretion Depends on Glycemia

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Context: Single-nucleotide polymorphisms (SNPs) within the *G6PC2* locus are associated with fasting glucose and insulin secretion. These SNPs are not associated with type 2 diabetes risk.

Objective: Our objective was to investigate whether the impact of the SNP on variables of glucose-stimulated insulin secretion is influenced by glucose tolerance status.

Design, Setting, Participants, and Intervention: In this cross-sectional study, we genotyped 1505 healthy Caucasian subjects [normal glucose tolerance (NGT), 1098; impaired glucose tolerance (IGT)/impaired fasting glucose (IFG), 407] for SNP rs560887 within the *G6PC2* locus. A subgroup of 326 subjects underwent an iv glucose tolerance test, and 512 participants took part in a hyperinsulinemic-euglycemic clamp. For replication, SNP rs560887 was genotyped in 457 subjects (NGT, 265; IGT, 192) from four independent German and Dutch studies who underwent a hyperglycemic clamp.

Main Outcome Measure: Insulin secretion was evaluated.

Results: Carriers of the major G-allele exhibited increased fasting glycemia ($P < 0.0001$). Insulin sensitivity and secretion were not associated with the SNP ($P \geq 0.06$). Glucose tolerance status and genotype interacted on insulin secretion ($P = 0.036$), such that in NGT subjects, the minor A-allele of rs560887 was associated with decreased insulinogenic index ($P = 0.044$), which was not the case in subjects with IFG/IGT ($P = 1.0$). During the iv glucose tolerance test, an association of A-allele carriers with decreased first-phase insulin secretion was also observed only in NGT subjects ($P = 0.0053$). Likewise, in the hyperglycemic clamp group, the A-allele was associated with decreased first-phase insulin secretion only in the NGT group ($P = 0.022$) but not in the IGT group.

Conclusions: The effects of hyperglycemia on insulin secretion override the more subtle effects of genetic variation in the *G6PC2* locus on insulin secretion. (***J Clin Endocrinol Metab*** **95: E479–E484, 2010)**

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Abbreviations: $AUC_{Ins0-10}$, Area under the curve for insulin 0–10 min; BMI, Body mass index; GWA, genome-wide association; HbA1c, glycosylated hemoglobin; IFG, impaired fasting glucose; IGI, insulinogenic index; IGRP, islet-specific glucose-6-phosphatase catalytic subunit-related protein; IGT, impaired glucose tolerance; ivGTT, iv glucose tolerance test; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; P_{dom}, *P* value for dominant inheritance model; P_{add}, *P* value for additive inheritance model; SNP, single-nucleotide polymorphism; T2DM, type 2 diabetes mellitus.

Type 2 diabetes mellitus (T2DM) is a multifactorial disease. Environmental factors (physical inactivity, sedentary lifestyle) and genetic background play an important role in the pathogenesis. By now, more than 25 gene variants are known to be associated with a higher T2DM risk (1).

Chronic hyperglycemia, insulin resistance, and β-cell dysfunction are main characteristics of this disease. However, most of the single-nucleotide polymorphisms (SNPs) associated with T2DM affect insulin secretion, suggesting that the main genetic defect is β-cell failure (2).

In contrast, some genes seem to alter fasting blood glucose and insulin secretion but, interestingly, appear not to be associated with higher T2DM risk itself. The reason for this peculiar finding is still unknown.

One of those genes is *G6PC2*. Two independent genome-wide association (GWA) studies identified the major allele of SNP rs560887 within the *G6PC2* locus to be robustly associated with increased fasting glucose levels (3, 4). The effect was verified in other cohorts (5–11). In addition, two studies reported an association of the SNP with insulin secretion in response to glucose stimulation, such that the major G-allele, the one associated with higher fasting glucose, is associated with increased insulin secretion (7, 11). Although the reason for this unexpected finding is still unclear, it might potentially be explained by effects of this SNP on insulin sensitivity.

Because three major phenotypic features for T2DM might be affected by this SNP (*i.e.* increased glucose production, impaired insulin secretion, and impaired insulin sensitivity), it is surprising that *G6PC2* was not identified as a T2DM risk gene in large GWA studies.

Already many years before the disease becomes clinically manifest, fasting and postprandial glucose levels are elevated. Hyperglycemia *per se* is known to affect the insulin secretion capacity and the insulin response to glucose. This may obscure this SNP's association with T2DM in a general population.

Thus, we investigated whether impaired glucose control (prediabetes) influences the association of genetic variation in *G6PC2*. We studied insulin sensitivity and insulin secretion parameters in the entire cohort as well as after stratification by glucose tolerance status and glycosylated hemoglobin (HbA1c). Additionally, a German and Dutch replication cohort with hyperglycemic clamp studies was investigated. We furthermore tested glucose-stimulated insulin secretion in isolated human islets derived from carriers of *G6PC2* variation *in vitro*.

Participants and Methods

More detailed information is reported within the Supplemental Data (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Participants

In the oral glucose tolerance test (OGTT) cohort, we studied 1504 nondiabetic subjects. For replication, we studied 457 participants from four independent studies from The Netherlands and Germany (12). The clinical characteristics are shown in Supplemental Table 1.

Genotyping

Genotyping of *G6PC2* SNP rs560887 was performed using TaqMan assay (Applied Biosystems, Foster City, CA) or Sequenom platform.

Oral glucose tolerance test

A 75-g OGTT with glucose, insulin, and C-peptide measurements was performed.

Intravenous glucose tolerance test (ivGTT) and hyperinsulinemic-euglycemic clamp

A subset of 326 participants was studied by ivGTT and another subgroup of 512 subjects by a hyperinsulinemic-euglycemic clamp.

Hyperglycemic clamp

A replication cohort of 457 participants was studied using the hyperglycemic clamp technique (glucose level of 10 mmol/liter) (12).

Analytical procedures, calculations, and statistical analyses are reported in the Supplemental Data.

Human islet culture and incubation

Isolated human islets from five donors (two heterozygous and one homozygous for the A-allele of SNP rs560887) were obtained from the Laboratory of Isolation and Transplantation of Cells, University of Geneva/Faculty of Medicine (Centre Médical Universitaire) through the European Consortium for Islet Transplantation. Details are given in the Supplemental Data.

Power calculation

Calculations are reported in the Supplemental Data.

Results

Data from the OGTT, ivGTT, and hyperglycemic clamp in the overall cohort

The observed minor allele frequency for SNP rs560887 was 31% for the OGTT cohort and 32% for the hyperglycemic clamp group (HapMap-CEU 30%), which was in Hardy-Weinberg equilibrium ($P \geq 0.9$). No significant difference for gender, age, and body mass index (BMI) between the genotype groups was observed (all $P \geq 0.6$).

As expected, in the OGTT cohort, the common G-allele of SNP rs560887 was associated with increased fasting glucose (all $P < 0.0001$, Supplemental Table 2). SNP rs560887 was not associated with any of the three tested indices for insulin sensitivity, namely homeostasis model assessment for insulin resistance and OGTT- and clamp-derived insulin sensitivity index (all $P \geq 0.4$, Supplemental

Table 2). In the entire cohort, OGTT-derived insulin secretion as well as ivGTT-derived first-phase insulin secretion and hyperglycaemic clamp derived first- and second-phase insulin secretion were not significantly influenced by SNP rs560887 (Supplemental Table 2).

We evaluated the influence of glucose tolerance status on SNP effects by analysis of covariance and identified glucose tolerance status as a covariate significantly interacting with the genotype on insulin secretion: rs560887 × glucose tolerance status on insulin secretion [insulinogenic index (IGI), *P* value for dominant inheritance model (P_{dom}) = 0.0364]. Glucose tolerance status did not interact with genotype on insulin sensitivity or with genotype on fasting glucose (all $P_{dom} \geq 0.08$).

Data from the OGTT, ivGTT, and hyperglycemic clamp after stratification by glycemia

After stratification of the OGTT cohort according to glucose tolerance [normal glucose tolerance (NGT) *vs.* impaired fasting glucose (IFG)/impaired glucose tolerance (IGT)], the carriers of the minor A-allele showed decreased IGI only in the NGT group [*P* value for additive inheritance model (P_{add}) = 0.044] but not in the IFG/IGT group (P_{add} = 1.0, Table 1). These associations in the NGT group remained significant after additional adjustment for fasting glucose (rs560887, P_{add} = 0.008). Stratification of subjects in quartiles according to their HbA1c did show nominal association of SNP rs560887 with IGI only in the quartile with lowest HbA1c level (P_{dom} = 0.035).

In the participants that underwent an ivGTT, insulin secretion in carriers of the minor A-allele was again significantly lower in participants with NGT [area under the curve for insulin 0–10 min ($AUC_{Ins0-10}$):P_{dom} = 0.0014, Fig. 1C], whereas no differences were observed in those with IFG/IGT ($AUC_{Ins0-10}$:P_{dom} = 0.7, Fig. 1D). Glucose levels did not diverge between genotypes in both groups (all $P \geq 0.4$, Fig. 1, A and B, and data not shown).

In the cohort that took part in a hyperglycemic clamp study, we replicated the finding of decreased first-phase insulin secretion in NGT subjects carrying the minor A-allele ($P = 0.022$), which was not present in the IGT group (Supplemental Table 2). Second-phase insulin secretion showed no interaction with glucose tolerance and was not different between genotypes.

Data from *in vitro* studies

When measuring glucose-induced insulin secretion in isolated human islets from five subjects, we observed lower insulin secretion in islets derived from the carriers of the minor A-allele than in those of donors carrying the major G-allele (Supplemental Fig. 1).

Discussion

This study confirms the previous finding of the major G-allele of *G6PC2* rs560887 being significantly associated with higher fasting glucose (3–7, 10, 11); this was true for all subjects regardless of their glucose tolerance status. Our study also confirmed the previously observed decreased glucose-stimulated insulin secretion in carriers of the minor A-allele (7, 11) using OGTT-, ivGTT-, and hyperglycemic clamp-derived measures of insulin secretion. However, we found this decreased insulin secretion consistently only in subjects with NGT. Subjects with IGT/IFG in the different cohorts showed no effect of *G6PC2* genotype on insulin secretion regardless of the test used. Furthermore, human islets derived from carriers of the minor A-allele secreted less insulin after glucose stimulation *in vitro*.

One would expect that a lower than normal insulin secretion in carriers of the minor A-allele should lead to an increased risk for T2DM. However, *G6PC2* has not been identified as a T2DM risk gene in large GWA studies. In our study, subjects with IGT/IFG showed no SNP effect on glucose-stimulated insulin secretion, suggesting that long-term impaired glucose metabolism overrides the SNP effects on insulin secretion.

Because we observed the association with insulin secretion only in NGT subjects, we additionally stratified our cohort in quartiles according to HbA1c. Again, SNP effects on insulin secretion were observed only in subjects within the lowest HbA1c quartile (<5.0%). To avoid overlooking associations in the higher HbA1c groups due to low power, we pooled all participants with HbA1c higher than 5.0% and still did not detect any association.

The *G6PC2* gene encodes the enzyme islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP) (13, 14). IGRP probably acts as counter-player to glucokinase by dephosphorylating glucose-6-phosphate. This substrate cycle modulates glucose-stimulated insulin secretion (13, 15–17). Alterations in the substrate cycle due to variation in the *G6PC2* gene (and hence altered IGRP content or activity) may explain association with insulin secretion. Interestingly, dephosphorylation of glucose-6-phosphate toward glucose is enhanced in islets of animal models for T2DM (18, 19) and is accompanied by reduced glucose-induced insulin secretion (19). The situation in IFG/IGT subjects may be comparable. They might have altered substrate cycling and accordingly reduced insulin secretion *per se*, independent of genetically determined IGRP content or activity. This would explain how increased blood glucose levels blunt the effect of *G6PC2* genotype on decreased insulin secretion.

The finding of increased fasting glucose in carriers of the major G-allele of rs560887 might be explained by alterations

TABLE 1. Associations of *G6PC2* SNP rs560887 with anthropometrics, metabolic parameters, and insulin secretion in participants with NGT and in participants with IFG and/or IGT

	NGT				IFG/IGT			
SNP *G6PC2* SNP rs560887	**GG**	**GA**	**AA**	P_{add}	**GG**	**GA**	**AA**	P_{add}
OGTT								
n (female/male)	509 (344/165)	479 (313/166)	109 (72/37)		209 (142/67)	167 (107/60)	31 (21/10)	
Age (yr)	37 (36–38)	38 (36–39)	39 (36–41)	0.4	45 (43–47)	44 (42–46)	44 (39–49)	0.8
BMI (kg/m^2)	27.15 (26.55–27.75)	27.14 (26.55–27.72)	28.05 (26.78–29.33)	0.4	31.90 (30.59–33.20)	32.54 (31.08–34.00)	30.74 (27.95–33.54)	0.6
HbA1c (%)	5.25 (5.21–5.28)	5.21 (5.18–5.25)	5.25 (5.16–5.34)	0.3	5.54 (5.47–5.61)	5.55 (5.47–5.679	5.29 (5.11–5.46)	0.023
Fasting glucose (mmol/liter)	4.93 (4.90–4.97)	4.88 (4.84–4.92)	4.79 (4.72–4.87)	<0.0001	5.70 (5.63–5.76)	5.60 (5.52–5.679	5.31 (5.13–5.48)	<0.0001
Glucose 120-min OGTT (mmol/liter)	5.63 (5.53–5.73)	5.61 (5.52–5.71)	5.70 (5.47–5.93)	1.0	7.74 (7.50–7.98)	8.19 (7.97–8.41)	7.96 (7.45–8.46)	0.007
Fasting insulin (pmol/liter)	54.3 (50.4–58.1)	53.2 (49.4–57.1)	56.3 (47.8–64.9)	0.7	84.4 (74.3–94.5)	86.1 (77.3–94.8)	84.5 (64.8–104.2)	0.3
C-peptide 30-min OGTT (pmol/liter)	2036 (1964–2109)	1991 (1914–2070)	1939 (1766–2113)	0.033	2154 (2017–2291)	2154 (2001–2308)	2073 (1789–2358)	0.3
IGI ($\times 10^{-9}$)	166 (1529–181)	150 (139–162)	151 (105–196)	0.023	134 (117–150)	134 (117–151)	121 (92–150)	1.0
HOMA-IR (mU × mmol × liters^{-2})	2.01 (1.86–2.15)	1.94 (1.80–2.09)	2.03 (1.71–2.36)	0.3	3.63 (3.18–4.08)	3.62 (3.23–4.01)	3.37 (2.55–4.19)	0.8
OGTT-derived ISI (arbitrary units)	18.88 (17.89–19.86)	18.60 (17.70–19.49)	20.27 (17.56–22.98)	0.4	10.59 (9.73–11.45)	9.46 (8.51–10.42)	9.92 (8.04–11.81)	0.4
Euglycemic clamp								
n	179	172	43		55	56	7	
Clamp-derived ISI (AU)	0.091 (0.082–0.099)	0.098 (0.089–0.106)	0.095 (0.078–0.112)	0.6	0.063 (0.053–0.073)	0.049 (0.039–0.059)	0.061 (0.032–0.089)	0.036
ivGTT								
n	95	89	25		49	47	8	
First-phase insulin secretion (pmol/liter)	1027 (901–1154)	897 (767–1028)	834 (587–1080)	0.005	835 (651–1018)	912 (725–1100)	885 (431–1399)	0.9
Hyperglycemic clamp								
n	116	125	24		93	77	22	
First-phase insulin secretion (pmol/liter)	901 (815–995)	805 (728–890)	730 (630–847)	0.022	671 (570–790)	756 (627–912)	763 (608–957)	0.18
Second-phase insulin secretion (pmol/liter)	270 (242–300)	233 (210–258)	259 (226–296)	0.15	227 (192–268)	260 (218–310)	252 (200–317)	0.16

Data represent means and 95% confidence intervals. For statistical analysis, data were log-transformed. BMI was adjusted for age and gender. HbA1c, glucose and insulin levels, homeostasis model assessment of insulin resistance (HOMA-IR), and insulin sensitivity index (ISI) (OGTT and clamp derived) were adjusted for gender, age, and BMI. Indices of insulin secretion were adjusted for gender, age, BMI, and insulin sensitivity. Secretion indices of the hyperglycemic clamp studies were adjusted for age, gender, BMI, study center, and family relatedness.

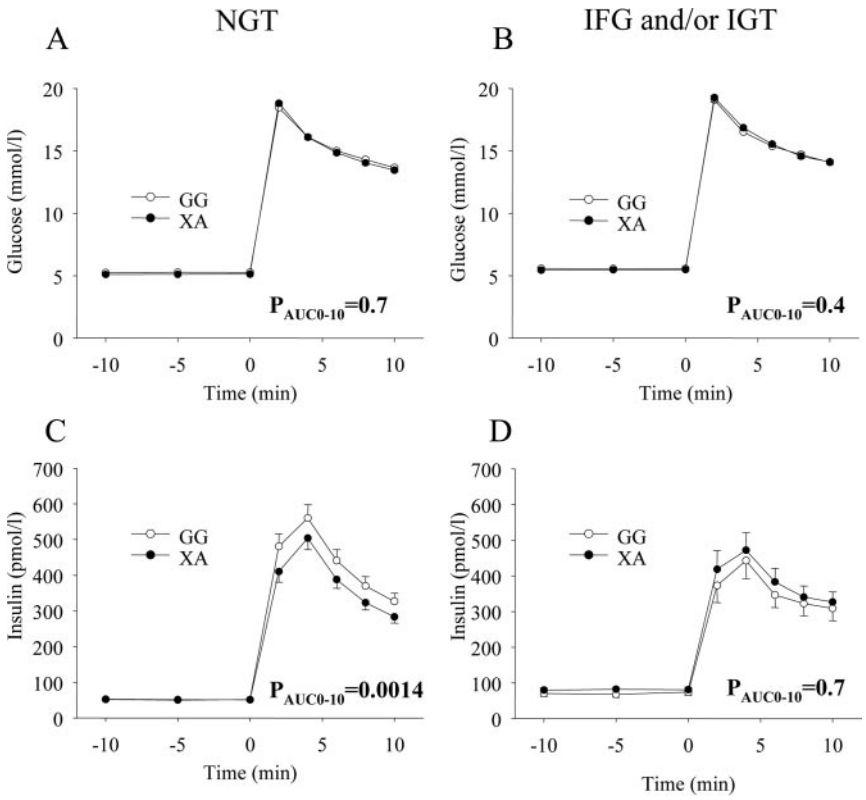

FIG. 1. Plasma glucose and insulin concentrations during the ivGTT in carriers of SNP rs560887 within the *G6PC2* gene region with NGT (A and C) or with IFG and/or IGT (B and D). Data are given as means ± SEM. A glucose bolus was given at time 0 min. *P* values (dominant model) for AUC of the 10 min after glucose injection adjusted for gender, age, BMI, and insulin sensitivity are given. ○, Homozygous carriers of the major allele; ●, heterozygous and homozygous carriers of the minor allele.

in insulin sensitivity or insulin secretion. Because none of the insulin sensitivity indices was different between genotypes (see Supplemental Table 2), decreased insulin sensitivity is unlikely to cause the significantly increased (but still in the normal range) fasting glucose in G-allele carriers. Insulin secretion is increased in NGT carriers of the major G-allele, and therefore changes in β-cell function cannot account for the higher fasting glucose. In addition, we tested whether SNP effects are independent by additionally adjusting fasting glucose for insulin secretion and vice versa. Because 1) the associations were still significant after the adjustments and 2) SNP effects on fasting glucose were observed independently of the glucose tolerance status whereas those on insulin secretion were present only in the NGT group, we believe that the associations with fasting glucose and glucose-stimulated insulin secretion are caused by independent mechanisms. One recent study reported that the rs560887 G-allele is associated with increased basal hepatic glucose production (7), which may be the most plausible explanation for the increased fasting glycemia. Recently, it has been shown that a small increase in fasting glucose was not associated with a significant increase in the incidence of T2DM (20). Accordingly, one might infer that the small increase in fasting glucose associated with the major G-allele of rs560887 is not sufficient to cause T2DM.

Among the limitations of our study is the fact that we could detect only relatively large effect sizes. In our OGTT cohort, the group of subjects with IFG/IGT is smaller compared with the NGT group. However, we replicated our findings in the hyperglycemic clamp group with a more balanced relation of NGT and IFG/IGT subjects. In addition, we were able to use different tests for insulin secretion in different populations including the ivGTT and the gold standard method, the hyperglycemic clamp. The SNP effects *in vitro* need to be studied in more donors, because our tissue culture results are of preliminary nature and do not allow final conclusions.

Taken together, our data confirm previously recognized associations of genetic variation within the *G6PC2* locus with fasting glucose and glucose-stimulated insulin secretion. Based on our findings, we postulate that these effects are independent.

Observing an association of these variants with insulin secretion only in NGT subjects and in subjects with HbA1c below 5% strengthens the hypotheses that the glucometabolic state and long-term glucose control influence SNP effects. Increasing glycemia seems to blunt SNP effects on insulin secretion, thus making those effects irrelevant in the further development toward T2DM.

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