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Common Variants Associated to Type 2 Diabetes in the Italian Population

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Abstract

Genome-wide association studies have identified numerous genetic variants for type 2 diabetes (T2D). Most genetic loci discovered to date were studied in Caucasians or Asian ancestry, however, there are no data regarding a quite large Italian sample. Therefore, we investigated T2D genetic susceptibility of 143 single nucleotide polymorphisms (SNPs) within 30 genes involved in glucose metabolism in a large Italian case-control study. For the study, 1875 Caucasian patients were selected from three Italian cohorts. Age, gender, BMI and fasting plasma glucose (FPG) values were collected. Population was split in cases and controls based on FPG values or T2D diagnosis. T2D subjects and whom with FPG higher that 126 mg/dL were recruited as cases whereas subjects with normal values of FPG were considered controls. In each subject 143 SNPs were genotyped. To evaluate the association between genetic variations and diabetes status, a logistic regression analysis, adjusted for age, sex and BMI, was performed. Overall, 948 (50.6%) had T2D. Twenty out of 143 variants within 11 different genes resulted significantly associated to T2D. Four of them were located into *TCF7L2* gene and presented the highest odd ratio (from 1.42 to 1.57). At least two SNPs were located within *KCNJ11*, *WFS1*, *ABCC8*, *JAZF1* and *HNF1B* genes and one SNP each was identified in *ADAMTS9*,

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IGF2BP2, *FTO*, *G6PC2* and *GCK* genes. Our findings support the role of 11 genes involved in glucose homeostasis in T2D risk development in a large Italian population. We found that such genetic information may be advantageous for predicting T2D.

Keywords

T2D, Genetics, Susceptibility, SNPs, Variants

1. Introduction

Type 2 diabetes (T2D) is a worldwide disease and it is expected to affect more than 629 million people by 2045 [1]. Type 2 diabetes is a complex disease, characterized by the interplay between environmental and genetic factors, and it is mainly determined by impaired beta cell function and/or insulin sensitivity [2].

In the past years, many studies have been conducted in order to unravel the genetic background of type 2 diabetes. Before 2007, candidate and linkage approaches lead to identify a small number of associated loci (*PPARG*, *KCNJ11*, *CAPN10*, *WFS1*, *IRS1* and *TCF7L2*) [3] [4]. From 2007 to present day, the advent of high-throughput genotyping technology, such as Genome Wide Association (GWA) Scan, increased the number of T2D associated loci, identified in different ethnic groups, up to over 240 genetic risk loci with about 400 independent association signals [5] [6] [7]. Initially, the first GWA studies lead to replicate the already known associated SNPs and to identify at least six novel T2D loci (*CDKN2A*/2B, *IGF2BP2*, *CDKAL1*, *HEEX*, *SLC30A8*) [8] [9] [10] [11]. The number of candidate polymorphisms further increased in the following years as a result of other GWA and meta-analysis studies that added *KCNQ1*, *CDC123*, *CAMK1*, *JAZF1*, *THADA*, *TSPAN8*, *ADAMTS9*, *NOTCH2*/*ADAM30* to the list [12] [13] [14] [15]. In 2010, Voight and collaborators discovered other T2D associated loci (*ARAP1*, *BCL11A*, *ZBED3*, *KLF14*, *TP53INP1*, *CHCHD9*, *CENTD2-ARAP1*, *HMGA2*, *ZFAND6*, *PRC1*, *TLE4* and *DUSP9*) and interestingly, among them, there were also two MODY genes (*HNF1A* and *HNF4A*) [16]. Previously published papers already reported an effect of SNPs located into MODY genes (*HNF4A*, *PDX1*, *NEUROD1*, *KLF11*, *GCK*, *CEL*) on type 2 diabetes, suggesting an influence of these monogenic diabetes loci also on the common form of the disease [17] [18] [19] [20]. Subsequent studies expanded their investigation to the genetic background of type 2 diabetes related traits, such as fasting plasma glucose and obesity, and they discovered a number of associated loci (*ADCY5*, *DGKB*, *GCK*, *GCKR*, *MTNR1B*, *PROX1*, *BCDIN3D*/*FAIM2*, *AIF1*/*NCR3*, *FTO*, *GNPDA2*, *MCR4*, *NEGR1*, *SFRS10*, *SH2B1* and *TMEM18*) [21]-[26]. More recently many other polymorphisms have been added to the list of T2D associated loci reaching a number of over 400 common variants involved in this disease susceptibility [6] [7] [27].

Despite the high number of associated loci, genetics can explain less than 20%

of type 2 diabetes heritability [28]. Moreover, investigating the role of genetics on T2D pathophysiological phenotypes, such as impaired beta cell function and insulin sensitivity, researchers found that insulin secretion was much more genetically determined than insulin action [16] [29] [30] [31] [32] [33]. Most of the GWA and meta-analysis studies have been conducted in Caucasians or Asian ancestry, however, as far as we know, there are no data regarding a quite large Italian sample. Thus, in this study, we aimed to genotyped 143 polymorphisms on 1875 Italian subjects (927 controls and 948 diabetic patients) in order to investigate their association with type 2 diabetes.

2. Methods

2.1. The INCIPE Study

INCIPE study (Initiative on Nephropathy, of relevance to public health, which is Chronic, possibly in its Initial stages, and carries a Potential risk of major clinical Endpoints) included 6200 patients, all Caucasians, ≥40-years old by January 1, 2006, randomly chosen from the lists of patients of 62 randomly selected general practitioners (GPs) based in four geographical areas in the Veneto region, Italy. In this study we reported data collected in 795 subjects, belonging to the INCIPE population and randomly selected. Enrolment and clinical examination were performed locally in four units, by trained medical doctors. After written informed consent was obtained, each participant completed a self-administered questionnaire (e.g., family and personal medical history, pharmacologic treatments, and smoking habits). Standard clinical parameters were assessed in all patients. Blood and urine samples were collected for each patient and processed at the Verona General Hospital, Central Laboratory [34].

2.2. GENFIEV Study

The GENFIEV study is a multicentre nationwide Italian study designed to recruit individuals with impaired glucose regulation (IGR) in the attempt to identify phenotypic and genotypic features that may allow the identification of subjects at high risk for T2D (http://clinicaltrials.gov/ct2/show/NCT00879801?term=GENFIEV&rank=1) [35]. The study was approved by Institutional Review Boards, and all subjects gave written informed consent before entering the study. In this study we reported data collected in 439 subjects, belonging to the GENFIEV study. All subjects underwent a standardised medical history, physical examination and an OGTT (75 g) to assess beta cell function, as previously described [36]. Biochemical parameters were determined by standard methods on Roche-Modular Autoanalyzer (Milan, Italy). Serum C-peptide and insulin concentrations were measured centrally in the Pisa laboratory by immunoassay (Immulite, DPC; Los Angeles, CA, USA). The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated for all subjects as follows: [insulin (mU/L)·glucose (mg/dL)]/22.5 and used as a fasting biomarker of insulin resistance [37].

2.3. Verona Newly Diagnosed Type 2 Diabetes Study (VNDS)

The VNDS is a cohort consisting of Caucasian patients with newly diagnosed type 2 diabetes, drug-naïve and GAD-antibodies negative (GAD65 < 1 KU/L). As of January 1, 2002, all patients with T2D referred to the Diabetes Clinic embedded into the Division of Endocrinology, Diabetes and Metabolic Diseases of the University and Hospital Trust of Verona and whose disease was diagnosed in the past 6 months were offered to participate in this study. Recruitment was ended on December 31, 2015 and a follow-up was then planned and is ongoing. A detailed description of the experimental design has been previously published [38] [39]. In this study we reported data collected in 641 subjects, belonging to the VNDS. Each subject gave informed written consent before participating in the research, which was approved by the Human Investigation Committee of the Verona City Hospital. Standard clinical parameters were assessed in all patients. Metabolic tests were carried out on two separate days in random order. On one day an OGTT (75 g) was performed to assess beta cell function, as previously described [36]. On a separate day, a euglycemic insulin clamp was performed to assess insulin sensitivity [38] [39]. Plasma glucose concentration was measured in duplicate with a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA, USA) or a YSI 2300 Stat Plus Glucose&Lactate Analyzer (YSI Inc., Yellow Springs, OH, USA), at bedside. Serum C-peptide and insulin concentrations were measured by chemiluminescence. Glycated hemoglobin and serum lipids were measured by standard in-house methods. GAD-antibodies were measured by immunoradiometry (CentAK, Medipan, Germany), according to manufacturer's instructions. The amount of glucose metabolized during the last 60 min of the clamp (M value) was computed with standard formulae [36].

In the GENFIEV and the VNDS a detailed assessment of beta cell function by state-of-art modelling of the glucose/C-peptide curves during the OGTT was performed, (details are reported in the **Supplementary Material** "Mathematical Modelling of Beta Cell Function Section" [41]-[47]).

2.4. Subjects Classification

Participants were classified as cases and controls on the basis of fasting plasma glucose values. Controls presented normal glucose tolerance having fasting blood glucose (FPG) ≤ 7 mmol/l (≤126 mg/dl), whereas, cases were T2D subjects having a clinical diagnosis of diabetes or an FPG value above 7 mmol/L (>126 mg/dL). Firstly, were identified T2D subjects and then was identified the control group selecting subjects as similar as possible for sex and gender.

2.5. Genotyping

A peripheral blood sample was collected from each patient and the DNA was extracted by standard salting out method. Genotypes were assessed by the high-throughput genotyping Veracode technique (Illumina Inc, CA), applying the GoldenGate Genotyping Assay according to manufacturer's instructions [48]. For

quality control (QC), only the samples and marker call rates > 90% were used. One hundred and thirty-three out of 143 polymorphisms have been successfully genotyped. Beyond the reported T2D associated polymorphisms, when possible, we selected also tag SNPs, through GEVALT software (GEnotype Visualization and ALgorithmic Tool) [49], in order to capture more that 90% of the common genetic variability of the genomic regions considered.

2.6. Statistical Analysis

Data are presented as medians and interquartile range, unless otherwise indicated. Hardy-Weinberg equilibrium was tested by chi-square test. Comparison between clinical and anthropometric features of cases and controls was performed by Mann-Whitney U test.

Type 2 diabetes association analyses, adjusted for age, gender and BMI, were carried out by logistic regression, using PLINK 1.07 [50]. Nominal statistical significance was declared at $p < 0.05$.

3. Results

3.1. Clinical Features of Cases and Controls.

The cohort was formed by 1875 subjects. Overall, 948 (50.6%) had diabetes: 99 subjects of GENFIEV cohort, 208 of INCIPE cohort and the whole VNDS population (n = 641). Median and interquartile range of age, BMI and fasting plasma glucose according to controls and cases are reported in Table 1 and Table 2, respectively. Not surprisingly, type 2 diabetes patients were older ($p = 0.01$), more obese ($p = 0.03$) and with higher fasting plasma glucose levels ($p < 0.001$) than controls.

3.2. Association of 133 Polymorphisms to Type 2 Diabetes

Ten polymorphisms failed the quality control and were not evaluated further. Allele distribution of the left 133 successfully genotyped polymorphisms was compatible with the Hardy-Weinberg equilibrium. A logistic regression analysis showed that 20 polymorphisms, located into 11 loci, were associated to type 2 diabetes, after adjustment for age, gender and BMI (Table 3). Four variants of *TCF7L2* gene displayed the strongest signal in term of both Odd Ratio (OR) and p-value ($p < 4 \times 10^{-7}$ or less). Other associated SNPs were located within *KCNJ11*, *WFS1*, *ADAMTS9*, *IGF2BP2*, *ABCC8*, *JAZF1*, *FTO*, *HNF1B*, *G6PC2* and *GCKR*

Table 1. Controls clinical features. Data are presented as median [I.Q. range].

Variable	Males	Females	All
Number (M/F)	517	410	927
Age (yrs)	57 [48 - 64]	54 [43 - 63]	56 [46 - 64]
BMI (kg/m²)	28 [26 - 31]	26 [29 - 32.9]	28.8 [26 - 31]
Fasting P-glucose (mmol/l)	5 [4.7 - 5.3]	4.9 [4.6 - 5.2]	5 [4.6 - 5.2]

Table 2. Type 2 diabetes subjects clinical features. Data are presented as median [I.Q. range].

Variable	Males	Females	All
Number (M/F)	623	325	948
Age (yrs)	59 [50 - 66]	62 [57 - 68]	60 [52 - 67]
BMI (kg/m^2)	29 [26 - 32.2]	29.9 [26.8 - 33.8]	29.2 [26.2 - 32.8]
Fasting P-glucose (mmol/l)	7.2 [6.3 - 8.1]	7.4 [6.4 - 8.5]	7.3 [6.4 - 8.3]

Table 3. Polymorphisms associated to type 2 diabetes. Data are presented as OR (95% CI) and adjusted for age, sex, BMI.

SNP	OR (95% CI) (minor allele)	p value	GENE
rs7903146	1.57 (1.36 - 1.81)	7.72×10^{-10}	TCF7L2
rs12255372	1.54 (1.33 - 1.78)	3.62×10^{-9}	TCF7L2
rs7901695	1.49 (1.29 - 1.72)	5.84×10^{-8}	TCF7L2
rs11196205	1.42 (1.24 - 1.62)	4.13×10^{-7}	TCF7L2
rs1002226	1.28 (1.11 - 1.47)	0.0006	KCNJ11
rs6446482	1.28 (1.11 - 1.48)	0.0007	WFS1
rs5219	1.26 (1.10 - 1.46)	0.001	KCNJ11
rs7648557	1.24 (1.09 - 1.42)	0.002	ADAMTS9
rs10010131	1.25 (1.08 - 1.43)	0.002	WFS1
rs6789741	1.27 (1.08 - 1.50)	0.005	IGF2BP2
rs7129639	1.21 (1.05 - 1.40)	0.007	ABCC8
rs864745	1.20 (1.05 - 1.38)	0.009	JAZF1
rs7204916	1.18 (1.03 - 1.35)	0.016	FTO
rs7501939	1.18 (1.03 - 1.35)	0.018	HNF1B
rs4722760	1.21 (1.03 - 1.42)	0.023	JAZF1
rs7106053	1.20 (1.02 - 1.40)	0.027	ABCC8
rs13387347	1.18 (1.02 - 1.36)	0.027	G6PC2
rs780094	1.16 (1.02 - 1.33)	0.027	GCKR
rs1557780	1.17 (1.02 - 1.34)	0.032	JAZF1
rs2689	1.16 (1.01 - 1.33)	0.038	HNF1B

genes ($p < 0.038$). Results regarding all other analyzed polymorphisms were reported in the **Supplementary Material**, Table S1.

4. Discussion

In this study we tested the association of 133 polymorphisms, in part already identified as T2D associated loci and in part selected as tag SNP within loci of interest, with type 2 diabetes on 1875 Italian subjects (927 controls and 948 cases).

The novelty of the study is that, as far as we know, this is the first study that investigated a number of polymorphisms, already associated to type 2 diabetes or located into/close to genes with a possible biological role in the development of the disease, in a quite large Italian population, thus giving information about the allelic frequency of these SNPs in Italians subjects.

Not surprisingly, *TCF7L2* variants displayed the strongest association signals, and this was consistent with previously published data, reporting for rs7903146 the highest odd ratio (OR: 1.37) of all type 2 diabetes associated polymorphisms, in different ethnic groups [51] [52] [53]. Different mechanisms have been hypothesized in order to explain the biological role of *TCF7L2* in determining type 2 diabetes, particularly it could: 1) decrease beta cell proliferation and insulin secretion; 2) alter insulin process or release; 3) affect GLP1 signalling in beta cell [54]; 4) alter local chromatin structure in islet cells [55].

Three loci, reported in this study, have been previously associated to type 2 diabetes through candidate-gene approach: *KCNJ11* and *ABCC8*, both encoding two subunits of the potassium channel, an important protein involved in the insulin release process [56] [57]; and *WFS1*, which is involved in the Wolfram Syndrome, a monogenic disease characterized also by diabetes mellitus [58]. Particularly, variants in WFS1 have been linked to gut incretin hormones such as pancreatic glucose-dependent insulinotropic peptide sensitivity. Because endoplasmic reticulum stress has been recognized as contributing to insulin resistance in type 2 diabetes [59], the dissection of pathogenic mechanisms in monogenic ER stress-mediated β-cell loss may also contribute to the understanding of type 2 diabetes pathogenesis [60].

All other associated variants have been previously identified through GWA studies [3] [4] [5] [6] [7]. Many of them have a biological role that could explain their involvement in type 2 diabetes, even if the molecular mechanisms are not yet clear and further functional studies are needed: *IGF2BP2*, which binds IGF2 mRNA and influences pancreas development [3] [61]; *FTO*, the strongest obesity gene so far identified, which probably promotes diabetes onset through an effect on BMI [62]; *HNF1B*, which regulates gene transcription of insulin and other proteins involved in glucose metabolism [63]; finally *G6PC2*, belonging to the glucose-6-phosphatase catalytic subunit family, and *GCKR*, the glucokinase regulatory protein, both involved in glucose metabolism, previously associated to fasting glucose levels and type 2 diabetes [64]. Glucokinase and glucose-6-phosphatase are the molecular bases of the glucose/glucose-6-phosphate cycle, which directly affects the glucose homeostasis through insulin secretion. Notably, the association between *G6PC2* SNPs and FPG was reported only in non-diabetic population, but not in T2D cohorts [65].

Moreover, we previously demonstrated that *GCKR* variability may play a pathogenetic role in type 2 diabetes affecting insulin secretion [40]. These three genes could be considered as determinants of glucose homeostasis that finely regulate beta cell function [40] [64].

The biological function of the last two loci that we found associated to type 2

diabetes in our Italian population, *JAZF1* and *ADAMTS9*, and that have been already identified in previous GWAS, is not yet well known, thus it is difficult to hypothesize their possible functional mechanisms in type 2 diabetes [12] [13], even because contrasting results have been found [66]. We previously demonstrated that variations in *ADAMTS9* were related to insulin secretion and a recent study of Cheng and colleagues indicated a positive regulatory role of *TCF7L2* on endogenous *ADAMTS9* expression [63] [67]. *JAZF1* has been implicated in glucose and metabolism, and its overexpression could result in enhanced glucose tolerance and insulin sensitivity, reduced body weight gain, inhibited the expression of genes related to lipid metabolism and lipid accumulation in adipocytes [68] [69] [70] [71]. A recent study of Kobiita A. *et al.*, shows that impaired JAZF1 function in T2D contributes to ribosomal and ER stress, activation of apoptosis pathways, and ultimately β-cell demise [72].

5. Conclusion

In conclusion, we replicated the association of 11 loci with type 2 diabetes in an Italian population, further genetic and functional studies will be necessary to identify the causal variants, if any, located into these T2D-associated loci.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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Supporting Information

Common variants associated to type 2 diabetes in the Italian population.

Mathematical Modeling of Beta Cell Function

The analysis of the glucose and C-peptide curves during the OGTT follows the general strategy described in previous publications [41] [42] with some modifications and builds upon previous works from other laboratories [43] [44]. The kinetics of C-peptide is described with a two-compartment model, in which the two pools (1 and 2) exchange with each other and the irreversible loss of the hormone is from pool 1, the same where C-peptide concentration is measured. C-peptide kinetic parameters are computed according to the equations by Van Cauter *et al.* [45].

Herein are the equations describing the model of glucose induced insulin secretion during an OGTT:

$$\mathrm{d}cp_1(t)/\mathrm{d}t = \mathrm{ISR}(t) + cp_2 \cdot k_{12} - (k_{01} + k_{21}) \cdot cp_1 \tag{1}$$

where ISR = insulin secretion rate, cp_1 = C-peptide mass in the sampling (accessible) compartment, cp_2 = C-peptide mass in the remote compartment, k_{12} and k_{21} = rate constants of the exchange between the two C-peptide compartments, and k_{01} = rate constant of the irreversible loss of C-peptide from the accessible compartment. Note that the values of the volume of distribution of C-peptide pool 1 (accessible compartment), k_{12}, k_{21}, and k_{01} are computed according to the equations by Van Cauter *et al.* [45].

$$\mathrm{ISR}(t) = \mathrm{BSR} + \mathrm{DSR}(t) + \mathrm{PSR}(t) \tag{2}$$

where BSR = basal insulin secretion rate, DSR = insulin secretion rate due to the derivative (or dynamic) component, and PSR = insulin secretion rate due the proportional (or static) component.

$$\mathrm{BSR} = CP_{ss} \cdot V_1 \cdot k_{01} \tag{3}$$

where CP_{ss} is basal C-peptide concentration and V_1 is the volume of the accessible compartment of C-peptide.

From the modeling viewpoint, DSR(t) and PSR(t) are the components which in intravenous glucose tolerance tests or hyperglycemic clamps describe classical first phase insulin secretion and second phase insulin secretion, respectively. Furthermore, from a physiological viewpoint, the sum of BSR and PSR(t) describes the relationship linking glucose concentration and insulin secretion rate, in the absence of the derivative component (DSR).

DSR(t) and PSR(t) are mathematically defined as follows:

$$\mathrm{DSR}(t) = X_1(t) \cdot \tau^{-1} \tag{4}$$

$$\mathrm{d}X_1(t)/\mathrm{d}t = \sigma_1 \cdot \left[\mathrm{d}G(t)/\mathrm{d}t\right] / \left[\log(1.1+t)\right] - X_1(t) \cdot \tau^{-1} \quad \text{if } \mathrm{d}G(t)/\mathrm{d}t > 0 \tag{5}$$

$$\mathrm{d}X_1(t)/\mathrm{d}t = -X_1(t) \cdot \tau^{-1} \quad \text{if } \mathrm{d}G(t)/\mathrm{d}t \le 0 \tag{6}$$

where σ_1 = glucose sensitivity of derivative control of insulin secretion, G = plasma glucose concentration, X_1 = C-peptide (insulin) mass made available for

the derivative component of insulin secretion, τ = time constant of the derivative component of insulin secretion, and the term log(1.1 + t) accomodates the time-associated decline of σ_1 documented in humans during a hyperglycemic stimulus [46].

$$\mathrm{PSR}(t) = X_2(t) \cdot \delta^{-1} \tag{7}$$

$$\mathrm{d}X_2(t)/\mathrm{d}t = \sigma_2 \cdot \left[G(t) - \theta\right] - X_2(t) \cdot \delta^{-1} \tag{8}$$

where σ_2 = glucose sensitivity of the proportional component of insulin secretion, X_2 = C-peptide (insulin) mass made available for the proportional component of insulin secretion, δ = time constant of the proportional component of insulin secretion, θ = glucose threshold above which the beta-cell responds with the proportional component of insulin secretion to plasma glucose concentration.

This model was implemented in the SAAM 1.2 software (SAAM Institute, Seattle, WA) [47] to estimate its unknown parameters. Numerical values of the unknown parameters were estimated by using nonlinear least squares. Weights were chosen optimally, *i.e.*, equal to the inverse of the variance of the measurement errors, which were assumed to be additive, uncorrelated, with zero mean, and a coefficient of variation (CV) of 6% - 8%. The unknown parameters of the model are: CP_{ss}, σ_1, τ, σ_2, δ, and θ. They were estimated with good precision, as shown by their CVs (**Supplemental** Table S1). Since in the GENFIEV Study the data set was to the time window 0' - 120', CPss was assumed to be equal to baseline C-peptide concentration in all subjects. For the same reasons, in those subjects of the GENFIEV Study in whom glucose levels did not go back close to baseline levels, θ was assumed to be equal to baseline glucose concentration.

Table S1. Association of the analysed polymorphisms with type 2 diabetes. Data are presented as OR (95% Confidence Interval).

SNP	OR (95% CI)	P value	GENE
rs4402960	1.15 (1 - 1.33)	0.05	IGF2BP2
rs1049817	1.15 (1 - 1.34)	0.06	GCKR
rs16857648	1.18 (0.99 - 1.39)	0.07	CACNA1E
rs7961581	1.14 (0.99 - 1.32)	0.07	TSPAN8
rs8122476	1.16 (0.98 - 1.36)	0.08	HNF4A
rs6547626	1.13 (0.97 - 1.31)	0.11	GCKR
rs12053195	1.18 (0.96 - 1.45)	0.12	NEUROD1
rs7756992	1.12 (0.97 - 1.3)	0.12	CDKAL1
rs4607103	1.12 (0.97 - 1.3)	0.13	ADAMTS9
rs6076472	1.12 (0.97 - 1.29)	0.13	TRIB3
rs2391489	1.11 (0.97 - 1.27)	0.13	JAZF1
rs12490804	1.12 (0.97 - 1.29)	0.14	ADAMTS9
rs1111875	1.11 (0.97 - 1.28)	0.14	HHEX

Continued

rs1873555	1.11 (0.96 - 1.28)	0.15	THADA
rs1801282	1.19 (0.93 - 1.51)	0.16	PPARG
rs10521304	1.1 (0.96 - 1.27)	0.16	FTO
rs8731	1.12 (0.95 - 1.32)	0.16	GCKR
rs7223387	1.11 (0.96 - 1.29)	0.17	HNF1B
rs17236708	1.1 (0.96 - 1.25)	0.18	FTO
rs11710969	1.12 (0.95 - 1.31)	0.18	PPARG
rs920779	1.14 (0.94 - 1.39)	0.19	ADAMTS9
rs4444493	1.13 (0.94 - 1.37)	0.20	KLF11
rs2384628	1.09 (0.95 - 1.25)	0.20	GCKR
rs13266634	1.1 (0.95 - 1.28)	0.22	SLC30A8
rs2184945	1.09 (0.95 - 1.25)	0.23	CACNA1E
rs4675095	1.15 (0.92 - 1.44)	0.23	IRS1
rs6115830	1.08 (0.95 - 1.24)	0.23	TRIB3
rs175338	1.11 (0.94 - 1.3)	0.24	CACNA1E
rs11024295	1.09 (0.95 - 1.25)	0.24	ABCC8
rs3905011	1.08 (0.95 - 1.24)	0.25	CACNA1E
rs10938397	1.08 (0.94 - 1.24)	0.25	GNPDA2
rs10797728	1.09 (0.93 - 1.28)	0.27	CACNA1E
rs6432052	1.1 (0.93 - 1.29)	0.29	KLF11
rs7923837	1.08 (0.94 - 1.24)	0.29	HHEX
rs1477092	1.08 (0.94 - 1.25)	0.29	FTO
rs708258	1.07 (0.94 - 1.23)	0.31	FTO
rs6781019	1.07 (0.94 - 1.24)	0.31	IGF2BP2
rs3753737	1.08 (0.93 - 1.25)	0.32	CACNA1E
rs2158254	1.07 (0.94 - 1.22)	0.32	HNF1B
rs9493119	1.15 (0.88 - 1.5)	0.32	ENPP1
rs4669522	1.08 (0.92 - 1.28)	0.35	KLF11
rs7635505	1.07 (0.93 - 1.23)	0.35	ADAMTS9
rs12071300	1.08 (0.91 - 1.29)	0.36	CACNA1E
rs882019	1.06 (0.93 - 1.22)	0.36	GCK
rs1036920	1.07 (0.92 - 1.25)	0.36	ADAMTS9
rs7578597	1.11 (0.89 - 1.37)	0.37	THADA
rs2868094	1.07 (0.92 - 1.23)	0.38	HNF4A
rs560887	1.07 (0.92 - 1.24)	0.39	G6PC2
rs13099634	1.07 (0.91 - 1.27)	0.42	PPARG
rs483109	1.06 (0.92 - 1.22)	0.42	G6PC2
rs4652679	1.06 (0.91 - 1.24)	0.45	CACNA1E

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rs1476891	1.06 (0.92 - 1.22)	0.45	GCK
rs6708660	1.06 (0.92 - 1.21)	0.45	THADA
rs11989843	1.06 (0.89 - 1.27)	0.49	SLC30A8
rs2708104	1.05 (0.91 - 1.21)	0.51	HNF1A
rs11897732	1.05 (0.91 - 1.2)	0.52	THADA
rs11523890	1.05 (0.9 - 1.22)	0.53	MTNR1B
rs10495899	1.05 (0.88 - 1.26)	0.56	THADA
rs6721191	1.04 (0.91 - 1.19)	0.57	KLF11
rs10830963	1.04 (0.9 - 1.22)	0.58	MTNR1B
rs4607517	1.05 (0.88 - 1.24)	0.58	GCK
rs1303722	1.04 (0.9 - 1.2)	0.58	GCK
rs4148638	1.04 (0.89 - 1.22)	0.59	ABCC8
rs6065726	1.04 (0.89 - 1.23)	0.60	HNF4A
rs6763887	1.04 (0.9 - 1.21)	0.61	IGF2BP2
rs9581927	1.04 (0.9 - 1.19)	0.61	PDX1
rs6130595	1.04 (0.89 - 1.22)	0.61	HNF4A
rs689266	1.04 (0.9 - 1.21)	0.61	CEL
rs7310409	1.03 (0.9 - 1.19)	0.63	HNF1A
rs679931	1.04 (0.9 - 1.2)	0.63	CACNA1E
rs7623286	1.03 (0.9 - 1.18)	0.66	ADAMTS9
rs6939185	1.03 (0.9 - 1.19)	0.67	ENPP1
rs10774580	1.03 (0.9 - 1.18)	0.68	HNF1A
rs6548238	1.04 (0.88 - 1.22)	0.69	TMEM18
rs6139007	1.03 (0.89 - 1.2)	0.70	TRIB3
rs4148625	1.03 (0.89 - 1.18)	0.71	ABCC8
rs7102746	1.03 (0.9 - 1.17)	0.71	MTNR1B
rs1801262	1.03 (0.89 - 1.18)	0.72	NEUROD1
rs630288	1.03 (0.88 - 1.19)	0.73	CEL
rs11768607	1.02 (0.89 - 1.18)	0.75	GCK
rs10766406	1.02 (0.89 - 1.17)	0.76	ABCC8
rs6717980	1.02 (0.88 - 1.18)	0.76	GCKR
rs1801278	1.04 (0.8 - 1.34)	0.78	IRS1
rs9923233	1.02 (0.89 - 1.17)	0.78	FTO
rs2466296	1.02 (0.87 - 1.2)	0.79	SLC30A8
rs4656253	1.04 (0.77 - 1.4)	0.80	PEA15
rs9933107	1.02 (0.88 - 1.18)	0.80	FTO
rs8075185	1.02 (0.89 - 1.16)	0.81	HNF1B
rs1169302	1.02 (0.89 - 1.16)	0.83	HNF1A

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rs10923931	1.03 (0.8 - 1.32)	0.83	NOTCH2
rs853770	1.01 (0.88 - 1.17)	0.87	G6PC2
rs6031596	1.01 (0.88 - 1.16)	0.87	HNF4A
rs4897549	1.01 (0.87 - 1.18)	0.87	ENPP1
rs17832252	1.01 (0.84 - 1.22)	0.88	GCK
rs1169286	1.01 (0.88 - 1.16)	0.89	HNF1A
rs858340	1.01 (0.87 - 1.17)	0.89	ENPP1
rs12475700	1.01 (0.88 - 1.16)	0.89	G6PC2
rs1169303	1.01 (0.88 - 1.15)	0.90	HNF1A
rs558994	1.01 (0.87 - 1.17)	0.90	CACNA1E
rs6544647	1.01 (0.88 - 1.15)	0.91	THADA
rs7632	1.01 (0.88 - 1.15)	0.91	KLF11
rs17024486	1.03 (0.68 - 1.55)	0.91	NOTCH2
rs7265169	1.01 (0.81 - 1.26)	0.92	TRIB3
rs3110648	1.01 (0.85 - 1.2)	0.92	HNF1B
rs7589033	1.01 (0.87 - 1.16)	0.93	THADA
rs190	1.01 (0.88 - 1.16)	0.93	JAZF1
rs10505310	1.01 (0.85 - 1.19)	0.95	SLC30A8
rs9666752	1 (0.88 - 1.15)	0.95	MTNR1B
rs709149	1 (0.88 - 1.15)	0.95	PPARG
rs6445425	1 (0.88 - 1.15)	0.95	ADAMTS9
rs2253388	1 (0.87 - 1.16)	0.96	CACNA1E
rs8048396	1 (0.88 - 1.15)	0.98	FTO

There are two main physiological outputs of the model:

1) derivative control (units: $[\text{pmol}\cdot\text{m}^{-2}\ \text{BSA}]\cdot[\text{mmol}\cdot\text{l}^{-1}\cdot\text{min}^{-1}]^{-1}$): it is the amount of insulin secreted in response to a rate of glucose increase of 1 mmol/l per min which lasts for 1 minute;

2) stimulus-response curve linking glucose concentration (x axis) to insulin secretion rate (y axis): as explained above, it is the sum of BSR and PSR. With the purpose of avoiding artifactual increases in the power of statistical analyses, we used the stimulus-response curve at the pre-determined glucose concentrations of 5.5, 8.0, 11.0, 15.0 and 20.0 mmol/l.