SUPPLEMENTARY DATA

Supplementary Table 1. Search Strategy

Database	Terms
PubMed	(“diabetes mellitus, type 2”[mh] or (diabet*[tiab] and (“non-insulin dependent”[tiab] or type-2[tiab] or “type II”[tiab] or “type 2”[tiab])) or “glucose intolerance”[mh] or (“impaired glucose”[tiab] and (toleran*[tiab] or stat*[tiab] or respons*[tiab] or control*[tiab] or regul*[tiab] or metab*[tiab] or homest*[tiab])) or (“impaired fasting”[tiab] and (glucose[tiab] or glycaemi*[tiab] or glycemi*[tiab] or bloodglucose[tiab] or “blood glucose”[tiab])) or IGT[tiab] or IFG[tiab] or “glucose intolerance”[tiab] or “glucose intolerant”[tiab] or prediabet*[tiab] or “pre-diabetes”[tiab] or “pre-diabetics”[tiab]or “pre-diabetic”[tiab]) AND (“hypoglycemic agents”[mh] or “thiazolidinediones”[mh] or “glipizide”[mh] or “glyburide”[mh] or “metformin”[mh] or “acarbose”[mh] or “Dipeptidyl-Peptidase IV Inhibitors”[mh] or bromocriptine[mh] or “insulin, nph”[mh] or “Insulin/analogs and derivatives”[mh] or insulin[mh] or thiazolidinedione*[tiab] or pioglitazone[tiab] or rosiglitazone[tiab] or sulfonylurea*[tiab] or sulphonylurea*[tiab] or glipizide[tiab] or glyburide[tiab] or glimepiride[tiab] or glibenclamide[tiab] or biguanide*[tiab] or metformin[tiab] or “insulin secretagogues”[tiab] or meglitinide*[tiab] or repaglinide[tiab] or nateglinide[tiab] or “alpha-glucosidase inhibitors”[tiab] or “alpha-glucosidase inhibitor”[tiab] or acarbose[tiab] or miglitol[tiab] or sitagliptin*[tiab] or dpp-4[tiab] or dpp-iv[tiab] or exenatide[tiab] or bromocriptine[tiab] or nph[tiab] or “neutral protamine hagedorn”[tiab] or insulin[tiab] or glargine[tiab] or detemir[tiab] or aspart[tiab] or lispro[tiab] or amylin[tiab] or pramlintide[tiab] or colesevelam[tiab] or (oral*[tiab] AND (hypoglycemic[tiab] or hypoglycaemic[tiab] or anti-hyperglycemic[tiab] or anti-hyperglycaemic[tiab] or antihyperglycemic[tiab] or antihyperglycaemic[tiab] or anti-diabet*[tiab] or antidiabet*[tiab]))) AND ((allel*[tiab] or gene*[tiab] or genotyp*[tiab]) and (polymorphi*[tiab] or variant*[tiab] or variation*[tiab]) or pharmacogenetic*[tiab] or SNP[tiab]) AND English[lang] NOT (animal[mh] NOT human [mh]) NOT (letter[pt] or comment[pt] or editorial[pt])
EMBASE	('non insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus' or (diabet*:ti,ab and (“non-insulin dependent”:ti,ab or type-2:ti,ab or “type II”:ti,ab or “type 2”:ti,ab)) or 'impaired glucose tolerance'/exp or (“impaired glucose”:ti,ab and (toleran*:ti,ab or stat*:ti,ab or respons*:ti,ab or control*:ti,ab or regul*:ti,ab or metab*:ti,ab or homest*:ti,ab)) or (“impaired fasting”:ti,ab and (glucose:ti,ab or glycaemi*:ti,ab or glycemi*:ti,ab or bloodglucose:ti,ab or “blood glucose”:ti,ab)) or IGT:ti,ab or IFG:ti,ab or “glucose intolerance”:ti,ab or “glucose intolerant”:ti,ab or prediabet*:ti,ab or “pre-diabetes”:ti,ab or “pre-diabetics”:ti,ab or “pre-diabetic”:ti,ab) AND ('oral antidiabetic agent'/exp or 'thiazolidinedione'/exp or 'rosiglitazone'/exp or 'pioglitazone'/exp or 'glipizide'/exp or 'glyburide'/exp or 'glimepiride'/exp or 'chlorpropamide'/exp or 'tolbutamide'/exp or 'metformin'/exp or 'meglitinide'/exp or 'repaglinide'/exp or 'nateglinide'/exp or 'alpha glucosidase inhibitor'/exp or 'acarbose'/exp or 'miglitol'/exp or 'dipeptidyl peptidase IV inhibitor'/exp or 'sitagliptin'/exp or 'exendin 4'/exp or 'bromocriptine'/exp or 'colesevelam'/exp or 'isophane insulin'/exp or 'biphasic insulin'/exp or 'human insulin'/exp or 'insulin aspart'/exp or 'insulin detemir'/exp or 'insulin glargine'/exp or 'insulin lispro'/exp or 'long acting insulin'/exp or thiazolidinedione*:ti,ab or pioglitazone:ti,ab or rosiglitazone:ti,ab or sulfonylurea*:ti,ab or sulphonylurea*:ti,ab or glipizide:ti,ab or glyburide:ti,ab or glimepiride:ti,ab or glibenclamide:ti,ab or chlorpropamide:ti,ab or tolbutamide:ti,ab or biguanide*:ti,ab or metformin:ti,ab or “insulin secretagogues”:ti,ab or meglitinide*:ti,ab or repaglinide:ti,ab or nateglinide:ti,ab or “alpha-glucosidase inhibitors”:ti,ab or “alpha-glucosidase inhibitor”:ti,ab or

SUPPLEMENTARY DATA

	acarbose:ti,ab or miglitol:ti,ab or sitagliptin*:ti,ab or dpp-4:ti,ab or dpp-iv:ti,ab or exenatide:ti,ab or bromocriptine:ti,ab or colesevelam:ti,ab or nph:ti,ab or "neutral protamine hagedorn":ti,ab or insulin:ti,ab or glargine:ti,ab or detemir:ti,ab or aspart:ti,ab or lispro:ti,ab or amylin:ti,ab or pramlintide:ti,ab or (oral*:ti,ab AND (hypoglycemic:ti,ab or hypoglycaemic:ti,ab or anti-hyperglycemic:ti,ab or anti-hyperglycaemic:ti,ab or antihyperglycemic:ti,ab or antihyperglycaemic:ti,ab or anti-diabetic:ti,ab or anti-diabetes:ti,ab or antidiabet*:ti,ab))) AND ((allel*:ti,ab or gene*:ti,ab or genotyp*:ti,ab) and (polymorphi*:ti,ab or variant*:ti,ab or variation*:ti,ab) or pharmacogenetic*:ti,ab or SNP:ti,ab or 'genotype'/exp) AND [english]/lim NOT ([animals]/lim NOT [humans]/lim) NOT (letter:it or comment:it or editorial:it)
Cochrane	#1 ((diabet*:ti,ab,kw and ("non-insulin dependent":ti,ab,kw or type-2:ti,ab,kw or "type II":ti,ab,kw or "type 2":ti,ab,kw)) or ("impaired glucose":ti,ab,kw and (toleran*:ti,ab,kw or stat*:ti,ab,kw or respons*:ti,ab,kw or control*:ti,ab,kw or regul*:ti,ab,kw or metab*:ti,ab,kw or homest*:ti,ab,kw)) or ("impaired fasting":ti,ab,kw and (glucose:ti,ab,kw or glycaemi*:ti,ab,kw or glycemi*:ti,ab,kw or bloodglucose:ti,ab,kw or "blood glucose":ti,ab,kw)) or IGT:ti,ab,kw or IFG:ti,ab,kw or "glucose intolerance":ti,ab,kw or "glucose intolerant":ti,ab,kw or prediabet*:ti,ab,kw or "pre-diabetes":ti,ab,kw or "pre-diabetics":ti,ab,kw or "pre-diabetic":ti,ab,kw) #2 (thiazolidinedione*:ti,ab,kw or pioglitazone:ti,ab,kw or rosiglitazone:ti,ab,kw or sulfonylurea*:ti,ab,kw or sulphonylurea*:ti,ab,kw or glipizide:ti,ab,kw or glyburide:ti,ab,kw or glimepiride:ti,ab,kw or glibenclamide:ti,ab,kw or chlorpropamide:ti,ab,kw or tolbutamide:ti,ab,kw or biguanide*:ti,ab,kw or metformin:ti,ab,kw or "insulin secretagogues":ti,ab,kw or meglitinide*:ti,ab,kw or repaglinide:ti,ab,kw or nateglinide:ti,ab,kw or "alpha-glucosidase inhibitors":ti,ab,kw or "alpha-glucosidase inhibitor":ti,ab,kw or acarbose:ti,ab,kw or miglitol:ti,ab,kw or sitagliptin*:ti,ab,kw or dpp-4:ti,ab,kw or dpp-iv:ti,ab,kw or exenatide:ti,ab,kw or bromocriptine:ti,ab,kw or colesevelam:ti,ab,kw or nph:ti,ab,kw or "neutral protamine hagedorn":ti,ab,kw or insulin:ti,ab,kw or glargine:ti,ab,kw or detemir:ti,ab,kw or aspart:ti,ab,kw or lispro:ti,ab,kw or amylin:ti,ab,kw or pramlintide:ti,ab,kw or (oral*:ti,ab,kw AND (hypoglycemic:ti,ab,kw or hypoglycaemic:ti,ab,kw or anti-hyperglycemic:ti,ab,kw or anti-hyperglycaemic:ti,ab,kw or antihyperglycemic:ti,ab,kw or antihyperglycaemic:ti,ab,kw or anti-diabetic:ti,ab,kw or anti-diabetes:ti,ab,kw or antidiabet*:ti,ab,kw))) #3 ((allel*:ti,ab,kw or gene*:ti,ab,kw or genotyp*:ti,ab,kw) and (polymorphi*:ti,ab,kw or variant*:ti,ab,kw or variation*:ti,ab,kw) or pharmacogenetic*:ti,ab,kw or SNP:ti,ab,kw) #4 (#1 AND #2 AND #3)

SUPPLEMENTARY DATA

Supplementary Table 2. Key journals included in manual search of tables of contents

Acta Pharmacol Sin
Br J Clin Pharmacol
Clin Pharmacol Ther
Diabet Med
Diabetes
Diabetes Care
Diabetes Res Clin Pract
Diabetes, Obesity and Metabolism
Diabetologia
Eur J Clin Pharmacol
Horm Metab Res
Int J Clin Pract
J Clin Endocrinol Metab
Pharmacogenet
The Pharmacogenomics Journal

SUPPLEMENTARY DATA

Supplementary Table 3. FDA-approved medications for type 2 diabetes at time of study inception

Sulfonylureas
chlorpropamide
tolbutamide
glipizide
glyburide/glibenclamide
glimepiride
Metformin
Thiazolidinediones
rosiglitazone
pioglitazone
Meglitinides
repaglinide
nateglinide
α glucosidase inhibitors
acarbose
miglitol
Sitagliptin
Exenatide
Bromocriptine
Colesevelam
Amylin-based
amylin
pramlintide
Insulin

SUPPLEMENTARY DATA

Supplementary Table 4. Interaction between metformin and selected SNPs for incident diabetes or attainment of HbA1c <7%

Author	Gene	SNP	Outcome	Follow up	Variant 1	Referent variant	Adjusted HR (95% CI)
Metformin transporters in hepatocytes							
Zhou, 2009 (1)	*SLC22A1*	rs4646281	HbA1c <7%	18 mo	Deletion	A	Adjusted OR: 0.98
Zhou, 2009 (1)	*SLC22A1*	rs12208357	HbA1c <7%	18 mo	T	C	Adjusted OR: 1.16[a]
Jablonski, 2010 (2)	*SLC22A1*	rs683369	DM	3.2 yrs	G	C	**Metformin: 1.45 (1.12 to 1.88)**
							Placebo: 0.99 (0.77 to 1.27)
Tkac, 2013 (3)	*SLC22A1*	rs622342	HbA1c	6 mo	AA, AC, CC		AA: -0.64% (-7 mmol/mol), AC: -0.69% (-7.5 mmol/mol), CC: -0.68% (-7.4 mmol/mol)
Jablonski, 2010[b] (2)	*SLC22A2*	rs662301	DM	3.2 yrs	T	C	**Metformin: 1.57 (1.09 to 2.27)**
							Placebo: 0.78 (0.49 1.22)
Florez, 2012 (4)	*SLC22A2*	rs11920090	FG	1 yr	T	A	P for interaction =0.88
Tkac, 2013 (3)	*SLC22A2*	rs316019	HbA1c	6 mo	GG, GT, TT		GG: -0.69% (-7.5 mmol/mol), GT: -0.92% (-10.1 mmol/mol)
Choi, 2011 (5)	*SLC22A2*	rs316019	HbA1c	160 days	GG	GT, TT	GG: -0.14% (-1.5 mmol/mol), GT/TT: -0.13% (-1.4 mmol/mol)
Jablonski, 2010[b] (2)	*SLC47A1*	rs8065082	DM	3.2 yrs	T	C	**Metformin: 0.78 (0.64 to 0.96)**
							Placebo: 1.15 (0.97 to 1.37)
Choi, 2011 (5)	*SLC47A1*	rs2289669	HbA1c	160 days	GG, GA	AA	GG: -0.14% (-1.5 mmol/mol), GA: -0.12% (-1.3 mmol/mol), AA: -0.17% (-1.9 mmol/mol)
Tkac, 2013 (3)	*SLC47A1*	rs2289669	HbA1c	6 mo	GG, GA, AA	N/A	GG: -0.61% (-6.7 mmol/mol), GA: -0.52% (-5.7 mmol/mol), AA: -1.10% (-12.0 mmol/mol)
AMPK pathway/Gluconeogenesis							
Jablonski, 2010[b] (2)	*PRKAA1*	rs249429	DM	3.2 yrs	C	T	**Metformin: 0.89 (0.71 to 1.13)**
							Placebo 1.22 (1.01 to 1.46)

SUPPLEMENTARY DATA

Jablonski, 2010[b] (2)	*PRKAB2*	rs6690158	DM	3.2 yrs	T	C	**Metformin: 1.42 (0.85 to 2.36)**
							Placebo: 0.58 (0.33 to 1.03)
Jablonski, 2010[b] (2)	*PRKAA2*	rs9803799	DM	3.2 yrs	G	T	**Metformin: 0.66 0.43 to 1.02**
							Placebo: 1.17)0.85 to 1.62)
Zhou, 2011 (6)	*ATM*	rs11212617	HbA1c <7%	18 mo	C	A	**1.42 (1.26 to 1.62)**[a]
Florez, 2012 (7)	*ATM*	rs11212617	DM	1 yr	C	A	**Metformin: 1.17 (0.96 to 1.42, P=0.13)**
							Placebo: 0.84 (0.70 to 1.01, P=0.71)
							P for interaction = 0.04
Florez, 2012 (7)	*ATM*	rs11212617	Ln(FG)	1 yr	C	A	P for interaction =0.31
Florez, 2012 (7)	*ATM*	rs11212617	Ln(HbA1c)	1 yr	C	A	P for interaction =0.77
Jablonski, 2010[b] (2)	*STK11*	rs741765	DM	3.2 yrs	T	C	**Metformin: 0.82 (0.64 to 1.04)**
							Placebo: 1.17 (0.96 to 1.43)
Jablonski, 2010[b] (2)	*PPARA*	rs4253652	DM	3.2 yrs	G	A	**Metformin: 2.29 (1.10 to 4.76)**
							Placebo: 0.60 (0.27 to 1.33)
Jablonski, 2010[b] (2)	*PPARGC1A*	rs10213440	DM	3.2 yrs	C	T	**Metformin: 1.31 (1.03 to 1.66),**
							placebo: 0.76 (0.59 to 0.97)
Jablonski, 2010[b] (2)	*PCK1*	rs4810083	DM	3.2 yrs	T	C	**Metformin 0.84 (0.69 to 1.02)**
							Placebo: 1.14 (0.95 to 1.37
Insulin secretion							
Florez, 2007 (8)	*KCNJ11*	rs5219 (E23K)	DM	3 yrs			EE: 0.55 (0.42 to 0.71)
							EK: 0.89 (0.66 to 1.19)
							KK: 0.95 (0.54 to 1.67)
Jablonski, 2010[b] (2)	*KCNJ11*	rs7124355	DM	3.2 yrs	A	G	**Metformin: 1.25 (0.99 1.59)**
							Placebo: 0.84 (0.68 to 1.04)
Jablonski, 2010[b] (2)	*ABCC8*	rs4148609	DM	3.2 yrs	A	G	**Metformin: 0.79 (0.63 to 0.98)**
							Placebo: 1.24 (1.04 to 1.48)
Pearson, 2007 (9)	*TCF7L2*	rs12255372	HbA1c ≥7%	12 mo	TT, TG, GG		TT: 1.09 (0.63 to 1.91)[a]
							TG: 0.96 (0.70 to 1.33)[a]
Pearson, 2007 (9)	*TCF7L2*	rs12255372	Time to HbA1c <7%	12 mo			P=0.82 for log rank test across genotypes (TT, TG, GG)
Florez, 2006 (10)	*TCF7L2*	rs12255372	DM	3 yrs	TT	GG	P for interaction not significant

SUPPLEMENTARY DATA

Pearson, 2007 (9)	*TCF7L2*	rs7903146	HbA1c ≥7%	12 mo	TT, TC	CC	TT: 1.19 (0.69 to 2.02)[a]
							TC: 1.17 (0.85 to 1.61)[a]
Florez, 2006 (10)	*TCF7L2*	rs7903146	DM	3 yrs	TT	CC	P for interaction not significant
Florez, 2008 (11)	*WFS1*	rs734312	DM	3 yrs	AG	AA	Metformin: 1.29 (0.90 to 1.86)
							Placebo: 0.98 (0.72 to 1.33)
Florez, 2008 (11)	*WFS1*	rs734312	DM	3 yrs	GG	AA	Metformin: 1.39 (0.95 to 2.02)
							Placebo: 1.19 (0.87 to 1.63)
Florez, 2008 (11)	*WFS1*	rs10010131	DM	3 yrs	GA	GG	Metformin: 1.17 (0.86 to 1.58)
							Placebo: 0.97 (0.75 to 1.26)
Florez, 2008 (11)	*WFS1*	rs10010131	DM	3 yrs	AA	GG	Metformin: 1.21 (0.80 to 1.83)
							Placebo: 1.15 (0.78 to 1.71)
Florez, 2008 (11)	*WFS1*	rs752854	DM	3 yrs	GA	AA	Metformin: 1.11 (0.82 to 1.50)
							Placebo: 1.09 (0.84 to 1.40)
Florez, 2008 (11)	*WFS1*	rs752854	DM	3 yrs	GG	AA	Metformin: 1.18 (0.73 to 1.89)
							Placebo: 1.14 (0.73 to 1.79)
Moore, 2008 (12)	*CDKN2A/B*	rs10811661	DM	3 yrs	T	C	**Metformin: 0.81 (0.59 to 1.12)**
							Placebo: 1.22 (0.96 to 1.54)
Jablonski, 2010[b] (2)	*HNF4A*	rs11086926	DM	3.2 yrs	G	T	**Metformin: 1.81 (1.35 to 2.43**
							Placebo: 0.82 (0.61 to 1.11)
Jablonski, 2010[b] (2)	*HNF1B*	rs11868513	DM	3.2 yrs	A	G	**Metformin: 0.87 (0.65 to 1.16)**
							Placebo: 1.69 (1.36 to 2.10)
Florez, 2012 (4)	*GLIS3*	rs7034200	FG	1 yr	A	C	P for interaction =0.72
Florez, 2012 (4)	*G6PC2*	rs573225	FG	1 yr	A	G	P for interaction =0.96
Florez, 2012 (4)	*MADD*	rs7944584	FG	1 yr	A	T	**P for interaction =0.04**
Florez, 2012 (4)	*MTNR1B*	rs10830963	FG	1 yr	G	C	P for interaction =0.68
Florez, 2012 (4)	*ADCY5*	rs11708067	FG	1 yr	A	G	P for interaction =0.80
Insulin sensitivity							
Jablonski, 2010[b] (2)	*ADIPOR2*	rs758027	DM	3.2 yrs	C	T	**Metformin: 1.31 (0.76 to 2.29)**
							Placebo 0.34 (0.15 to 0.75)
Moore, 2009 (13)	*ENPP1*	rs1044498	DM	3 yrs	CC/CA	AA	**Metformin: 1.09 (0.78 to 1.53)**
							Placebo: 1.36 (1.02 to 1.80)
Jablonski, 2010[b] (2)	*CAPN10*	rs3792269	DM	3.2 yrs	G	A	**Metformin: 0.95 (0.70 to 1.28)**

SUPPLEMENTARY DATA

							Placebo: 1.61 (1.28 to 2.02)
Jablonski, 2010[b] (2)	*GCK*	rs2908289	DM	3.2 yrs	A	G	**Metformin: 1.29 (1.02 to 1.64)**
							Placebo: 0.86 (0.69 to 1.08)
Florez, 2012 (4)	*GCK*	rs917793	FG	1 yr	T	A	P for interaction = 0.07
Florez, 2012 (4)	*IRS1*	rs4675095	FG	1 yr	A	T	P for interaction =0.21
Florez, 2012 (4)	*IGF1*	rs855228	FG	1 yr	T	C	P for interaction =0.39
Florez, 2012 (4)	*GCKR*	rs780094	FG	1 yr	C	T	P for interaction =0.57
Energy Metabolism							
Jablonski, 2010[b] (2)	*MEF2A*	rs424892	DM	3.2 yrs	G	A	**Metformin: 1.43 (1.14 to 1.80)**
							Placebo: 0.88 (0.72 to 1.09)
Jablonski, 2010[b] (2)	*MEF2D*	rs6666307	DM	3.2 yrs	T	A	**Metformin: 2.15 (1.22 to 3.80)**
							Placebo: 0.54 (0.26 to 1.09)
Florez, 2012 (4)	*CRY2*	rs11605924	FG	1 yr	A	C	P for interaction =0.20
Other							
Jablonski, 2010[b] (2)	*ITLN2*	rs6701920	DM	3.2 yrs	A	G	**Metformin: 0.49 (0.17 to 1.40)**
							Placebo: 1.86 (1.19 to 2.91)
Jablonski, 2010[b] (2)	*GCG*	rs6733736	DM	3.2 yrs	G	A	**Metformin: 3.70 (1.56 to 8.80)**
							Placebo: 0.65 (0.20 to 2.13)
Jablonski, 2010[b] (2)	*PKLR*	rs17367421	DM	3.2 yrs	C	G	**Metformin: 1.21 (0.73 to 1.99)**
							Placebo: 0.47 (0.23 to 0.96)
Jablonski, 2010[b] (2)	*PPARGC1B*	rs741579	DM	3.2 yrs	G	A	**Metformin: 0.23 (0.03 to 1.62)**
							Placebo: 2.41 (1.08 to 5.37)
Dong, 2011 (14)	*SRR*	rs391300	FG	12 wks	GG	GA+AA	**GG: -2.3 mmol/l, GA/AA: -3.3 mmol/l; P =0.024**
Dong, 2011 (14)	*SRR*	rs391300	PPG	12 wks	GG	GA+AA	**GG: -5.7 mmol/l, GA/AA: -8.8 mmol/l; P =0.048**
Dong, 2011 (14)	*SRR*	rs391300	HbA1c	12 wks	GG	GA+AA	GG: -1.1% (-12.0 mmol/mol), GA/AA: -2.83% (-30.9 mmol/mol); P = 0.058
Florez, 2012 (4)	*PROX1*	rs340874	FG	1 yr	C	T	P for interaction =0.81
Florez, 2012 (4)	*DGKB*	rs2191349	FG	1 yr	T	G	P for interaction =0.79

SUPPLEMENTARY DATA

Florez, 2012 (4)	*ADRA2A*	rs10885122	FG	1 yr	G	T	P for interaction =0.82
Florez, 2012 (4)	*FADS1*	rs174550	FG	1 yr	T	C	P for interaction =0.58
Florez, 2012 (4)	*C2CD4B*	rs11071657	FG	1 yr	AA	AG	**P for interaction =0.04**

Abbreviations: FG, fasting glucose; DM, diabetes mellitus; yr, years; mo, months; wks, weeks; PPG, 2-hour glucose from oral glucose tolerance test

Note: Results in bold indicate significant difference by genotype (P <0.05) or significant interaction with genotype (P for interaction <0.05).

SUPPLEMENTARY DATA

Supplementary Table 5. Interaction between sulfonylureas and selected SNPs for glycemic outcomes

Author Year	SNP	Outcome	Follow up	Variant 1	Referent variant	Effect Measure	Result
TCF7L2							
Pearson, 2007 (9)	rs12255372	HbA1c ≥7%	12 mo	TT, GT	GG	Adjusted OR	TT: 2.16 (1.21 to 3.86), GT: 1.14 (0.78 to 1.68); additive model: T vs. G: 1.28 (P <0.05)
Pearson, 2007 (9)	rs7903146	HbA1c ≥7%	12 mo	TT, TC	CC	Adjusted OR	TT: 1.90 (1.09 to 3.33), TC: 1.23 (0.84 to 1.81); additive model: T vs. C 1.26 (P <0.05)
Pearson, 2007 (9)	rs12255372	Time to HbA1c <7%		TT	GG	HR	P=0.03 for log rank test across genotypes
KCNJ11							
Gloyn, 2001 (15)	rs5219 (E23K)	FG	12 mo			Mean change from baseline	No difference across genotype
Gloyn, 2001 (15)	rs1800467	FG	12 mo			Mean change from baseline	No difference across genotype
CYP2C9							
Suzuki, 2006 (16)	rs1057910	HbA1c	6 mo	1/1	1/3	Mean change from baseline	Greater decrease (P <0.05)
Becker, 2008 (17)	rs1799853	FG	≥ 180 days after drug initiation	1/2, 2/2	1/1	Mean change from baseline	Tolbutamide: -0.28 mmol/l (-0.07 to 0.67 mmol/l)
Becker, 2008 (17)	rs1057910	FG	≥ 180 days after drug initiation	1/3, 2/3	1/1	Mean change from baseline	Tolbutamide: -1.2 mmol/l (-2.8 to 0.28 mmol/l)

Abbreviations: SNP, single nucleotide polymorphisms; HbA1c, hemoglobin A1c; OR, odds ratio; mo, months; wks, weeks

SUPPLEMENTARY DATA

Supplementary Table 6. Interaction between repaglinide and selected SNPs for glycemic outcomes

Author, Year	SNP	Outcome	Follow up	Mean change from baseline by genotype
KCNJ11				
He, 2008 (18)	rs5219	HbA1c	6 mo	**GG: -1.52% (-16.6 mmol/mol), GA: -2.33% (-25.5 mmol/mol), AA: -2.65% (-29.0 mmol/mol)**
	rs5219	FG	6 mo	GG: -2.3 mmol/l, GA: -3.3 mmol/l, AA: -3.1 mmol/l
	rs5219	PPG	6 mo	**GG: -4.1 mmol/l, GA: -5.8 mmol/l, AA: -3.6 mmol/l**[a]
ABCC8				
He, 2008 (18)	rs1799854	HbA1c	6 mo	TT: -1.88% (-20.6 mmol/mol), TC: -2.14% (-23.4 mmol/mol), CC: -2.29% (-25.0 mmol/mol)
	rs1799854	FG	6 mo	TT: -2.7 mmol/l, TC: -2.9 mmol/l, CC: -3.4 mmol/l
	rs1799854	PPG	6 mo	TT: -4.3 mmol/l, TC: -5.2 mmol/l, CC: -5.1 mmol/l
KCNQ1				
Yu, 2011 (19)	rs2237892	HbA1c	48 wks	TT: -2.13% (-23.3 mmol/mol), CT: -2.01%(-22.0 mmol/mol), CC: -1.99% (-21.8 mmol/mol)
	rs2237892	FG	48 wks	TT: -4.4 mmol/l, CT: -2.5 mmol/l, CC: -2.3 mmol/l
	rs2237892	PPG	48 wks	TT: -7.5 mmol/l, CT: -4.2 mmol/l, CC: -4.3 mmol/l
	rs2237895	HbA1c	48 wks	AA: -2.17% (-23.7 mmol/mol), AC: -1.83% (-20.0 mmol/mol), CC: -2.11% (-23.1 mmol/mol)
	rs2237895	FG	48 wks	AA: -2.8 mmol/l, AC: -2.9 mmol/l, CC: -2.7 mmol/l
	rs2237895	PPG	48 wks	AA: -4.7 mmol/l, AC: -3.9 mmol/l, CC: -5.0 mmol/l
	rs2237897	HbA1c	48 wks	CC: -1.95% (-21.3 mmol/mol), CT: -2% (-21.9 mmol/mol), TT: -2.68% (-29.3 mmol/mol)
	rs2237897	FG	48 wks	CC: -2.4 mmol/l, CT: -2.2 mmol/l, TT: -4.2 mmol/l
	rs2237897	PPG	48 wks	CC: -4.0 mmol/l, CT: -4.6 mmol/l, TT: -8.4 mmol/l[a]
SLC30A8				
Huang, 2010 (20)	rs1326634	HbA1c	8 wks	CC: -1.57% (-17.2 mmol/mol), CT/TT: -2.11% (-23.1 mmol/mol)[,]
	rs1326634	FG	8 wks	CC: -1.9 mmol/l, CT/TT: -2.2 mmol/l
	rs1326634	PPG	8 wks	CC: -4.2 mmol/l, CT/TT: -4.6 mmol/l
	rs16889462	HbA1c	8 wks	**GG: -1.43% (-15.6 mmol/mol), GA: -3.19% (-34.9 mmol/mol)** [a,c]

SUPPLEMENTARY DATA

	rs16889462	FG	8 wks	**GG: -1.6 mmol/l, GA: -3.6 mmol/l[a]**
	rs16889462	PPG	**8 wks**	**GG: -3.2 mmol/l, GA: -8.4 mmol/l[a]**
Jiang, 2012 (21)	rs13266634	HbA1c	48 wks	CC: -2.21% (-24.2 mmol/mol), CT: -2.00% (-21.9 mmol/mol), TT: -1.61% (-17.6 mmol/mol)
	rs13266634	FG	48 wks	CC: -2.4 mmol/l, CT: -2.6 mmol/l, TT: -2.2 mmol/l
	rs13266634	PPG	48 wks	CC: -4.5 mmol/l, CT: -4.4 mmol/l, TT: -3.8 mmol/l
NOS1AP				
Qin, 2010 (22)	rs10494366	HbA1c	24 wks	GG: -2.07% (-22.6 mmol/mol), GT: -2.18% (-23.8 mmol/mol), TT: -1.61% (-12.7 mmol/l)
	rs10494366	FG	24 wks	GG: -2.9 mmol/l, GT: -2.9 mmol/l, TT: -3.5 mmol/l
	rs10494366	PPG	24 wks	GG: -5.4 mmol/l, GT: -4.9 mmol/l, TT: -5.7 mmol/l
NEUROD1/BETA2				
Gong, 2012 (23)	A45T	FG	8 wks	AA: -2.8 mmol/l, AT/TT: -1.0 mmol/l; P<0.01
	A45T	PPG	8 wks	AA: -6.7 mmol/l, AT/TT: -2.6 mmol/l; P<0.01
	A45T	HbA1c	8 wks	AA: -3.05% (-33.3 mmol/mol), AT/TT: -2.15% (-23.5 mmol/mol)
PAX4				
Gong, 2012 (23)	R121W	FG	8 wks	RR: -2.6 mmol/l, RW/WW: -1.0 mmol/l; P=0.053
	R121W	PPG	8 wks	RR: -6.6 mmol/l, RW/WW: -2.9 mmol/l; P=0.046
	R121W	HbA1c	8 wks	RR: -2.73% (-29.8 mmol/mol), RW/WW: -1.31% (-14.3 mmol/mol)
NAMPT				
Sheng, 2011 (24)	[-3186C/T]	FG	8 wks	CC: -2.6 mmol/l, CT: -2.0 mmol/l, TT: -1.7 mmol/l
	[-3186C/T]	PPG	8 wks	CC: -5.4 mmol/l, CT: -4.8 mmol/l, TT: -4.0 mmol/l
	[-3186C/T]	HbA1c	8 wks	CC: -2.04% (-22.3 mmol/mol), CT: -2.36% (-25.8 mmol/mol), TT: -0.93% (-10.2 mmol/mol)
UCP2				
Wang, 2012 (25)	rs659366	HbA1c	8 wks	**GG: -2.38% (-26.0 mmol/l), GA/AA: 1.49% (-16.3 mmol/mol)**
	rs659366	FG	8 wks	**GG: -2.7 mmol/l, GA/AA: -1.7 mmol/l**
	rs659366	PPG	8 wks	GG: -5.1 mmol/l, GA/AA: -4.3 mmol/l

Abbreviations: SNP, single nucleotide polymorphism; HbA1c, hemoglobin A1c; FG, fasting glucose; PPG, post-prandial glucose; mo, months; wks, weeks.

SUPPLEMENTARY DATA

Supplementary Table 7. Interaction between pioglitazone and selected SNPs for glycemic outcomes

Author, year	Gene	SNP	Outcome	Follow up	Mean change from baseline by genotype
Bluher, 2003 (26)	*PPARG2*	rs1801282 (Pro12Ala)	HbA1c	26 wks	Pro12Pro: -1.22% (-13.3 mmol/mol), Pro12Ala: -0.97% (-10.6 mmol/mol), Ala12Ala: -1.5% (-16.4 mmol/mol)
	PPARG2	rs1801282 (Pro12Ala)	FG	26 wks	Pro12Pro: -3.0 mmol/l, Pro12Ala: -3.2 mmol/l, Ala12Ala: -2.1 mmol/l
Pei, 2013 (27)	*PPARG2*	rs1801282 (Pro12Ala)	FG	12 wks	Pro12Pro: -1.2 mmol/l, Pro12Ala: -2.2 mmol/l; P =0.015
	PPARG2	rs1801282 (Pro12Ala)	PPG	12 wks	Pro12Pro: -2.6 mmol/l, Pro12Ala: -0.4 mmol/l
	PPARG2	rs1801282 (Pro12Ala)	HbA1c	12 wks	Pro12Pro: -0.75% (-8.2 mmol/mol), Pro12Ala: -0.39% (-4.3 mmol/mol); P =0.132
Saitou, 2010 (28)	*ACE*	rs1799752	HbA1c	24 mo	No difference by genotype
	MTHFR	rs1801133	HbA1c	24 mo	No difference by genotype
Pei, 2013 (27)	*PTPRD*	rs17584499	FG	12 wks	CC: -1.3 mmol/l, CT/TT: -1.3 mmol/l
	PTPRD	rs17584499	PPG	12 wks	CC: -3.2 mmol/l, CT/TT: -0.6 mmol/l; P =0.005
	PTPRD	rs17584499	HbA1c	12 wks	CC: -0.92% (-10.1 mmol/l), CT/TT: -0.61% (-6.7 mmol/mol)

Abbreviations: SNPs, single nucleotide polymorphisms; HbA1c, hemoglobin A1c; FG, fasting glucose; wks, weeks; mo, months

SUPPLEMENTARY DATA

Supplementary Table 8. Interaction between rosiglitazone and selected SNPs for glycemic outcomes

Author, year	SNP	Outcome	Follow up	Mean change from baseline by genotype
ABCA1				
Wang, 2008 (29)	rs2230806	HbA1c	48 weeks	GG: -2.09% (-22.8 mmol/mol), AG/AA: -1.73% (-18.9 mmol/mol)
	rs2230806	FG	48 weeks	GG: -2.8 mmol/l, AG/AA: -2.3 mmol/l
	rs2230806	PPG	48 weeks	GG: -4.7 mmol/l, AG/AA: -4.3 mmol/l
	rs4149313	HbA1c	48 weeks	CC: -1.84% (-20.1 mmol/mol), CT/TT: -1.84% (-20.1 mmol/mol)
	rs4149313	FG	48 weeks	CC: -2.2 mmol/l, CT/TT: -2.7 mmol/l
	rs4149313	PPG	48 weeks	CC: -4.2 mmol/l, CT/TT: -4.6 mmol/l
	rs2230808	HbA1c	48 weeks	RR: -1.76% (-19.2 mmol/mol), KR/KK: -1.88% (-20.6 mmol/mol)
	rs2230808	FG	48 weeks	RR: -2.4 mmol/l, KR/KK: -2.4 mmol/l
	rs2230808	PPG	48 weeks	RR: -4.4 mmol/l, KR/KK: -4.4 mmol/l
KCNQ1				
Yu, 2011 (19)	rs2237892	HbA1c	48 weeks	TT: -2.24% (-24.5 mmol/mol), CT: -1.83% (-20.0 mmol/mol), CC: -1.8% (-19.7 mmol/mol)
	rs2237892	FG	48 weeks	TT: -3.3 mmol/l, CT: -2.3 mmol/l, CC: -2.4 mmol/l
	rs2237892	PPG	48 weeks	TT: -6.7 mmol/l, CT: -4.3 mmol/l, CC: -4.2 mmol/l
	rs2237895	HbA1c	48 weeks	AA: -1.51% (-16.5 mmol/mol), AC: -2.07% (-22.6 mmol/mol), CC: -1.73% (-18.9 mmol/mol)
	rs2237895	FG	48 weeks	AA: -2.27 mmol/l, AC: -2.44 mmol/l, CC: -2.75 mmol/l
	rs2237895	PPG	48 weeks	AA: -5.39 mmol/l, AC: -3.67 mmol/l, CC: -4.21 mmol/l
	rs2237897	HbA1c	48 weeks	CC: -1.68% (-18.4 mmol/mol), CT: -1.9% (-20.8 mmol/mol), TT: -2.48% (-26.2 mmol/mol)
	rs2237897	FG	48 weeks	CC: -2.56 mmol/l, CT: -2.2 mmol/l, TT: -2.99 mmol/l
	rs2237897	PPG	48 weeks	CC: -3.69 mmol/l, CT: -4.94 mmol/l, TT: -6.3 mmol/l
SLC30A8				
Jiang, 2012 (21)	rs13266634	HbA1c	48 weeks	CC: -1.53% (-16.7 mmol/mol), CT: -2.14% (-23.4 mmol/mol), TT: -1.65% (-18.0 mmol/mol)
	rs13266634	FG	48 weeks	CC: -2.2 mmol/l, CT: -2.7 mmol/l, TT: -2.2 mmol/l
	rs13266634	PPG	48 weeks	CC: -3.2 mmol/l, CT: -5.3 mmol/l, TT: -4.9 mmol/l
RBP4				
Zhou, 2011 (30)	rs3758539	FG	12 weeks	GG: -2.9 mmol/l, GA/AA: -1.5 mmol/l[a]

	rs3758539	PPG	12 weeks	GG: -4.2 mmol/l, GA/AA: -3.6 mmol/l
	rs3758539	HbA1c	12 weeks	GG: -2.03% (-22.2 mmol/mol), GA/AA: -1.39% (-15.2 mmol/mol)
	rs10882283	FG	12 weeks	TT: -2.8 mmol/l, TG/GG: -2.1 mmol/l
	rs10882283	PPG	12 weeks	TT: -2.9 mmol/l, TG/GG: -3.2 mmol/l
	rs10882283	HbA1c	12 weeks	TT: 1.16% (-12.7 mmol/mol), TG/GG: -3.78% (-41.3 mmol/mol)[a]

Abbreviations: SNP, single nucleotide polymorphism; HbA1c, hemoglobin A1c; FG, fasting glucose; PPG, post-prandial glucose

SUPPLEMENTARY DATA

Supplementary Table 9. Interaction between acarbose and selected SNPs for diabetes risk

Author, year	SNP	Follow up	Variant 1	Referent	Effect Measure	Result
PPARA						
Andrulionyte, 2007 (31)	rs1800206	3.3 yrs	CG/GG	CC	Cumulative incidence	P for interaction <0.05
	rs1800206	3.3 yrs	CG/GG	CC	Adjusted OR	Acarbose: 0.75 (0.39 to 1.46)
						Placebo: 1.93 (1.05 to 3.58)
	rs4253776	3.3 yrs	AG/GG	AA	Cumulative incidence	P for interaction <0.05
	rs4253776	3.3 yrs	AG/GG	AA	Adjusted OR[a]	Acarbose: 1.70 (1.00 to 2.90)
						Placebo: 0.80 (0.50 to 1.26)
	rs4253623	3.3 yrs	AG/GG	AA	Cumulative incidence	P for interaction > 0.05
	rs135547	3.3 yrs	CG/GG	CC	Cumulative incidence	P for interaction > 0.05
	rs135542	3.3 yrs	TC/CC	TT	Cumulative incidence	P for interaction > 0.05
	rs135539	3.3 yrs	AC/CC	AA	Cumulative incidence	P for interaction > 0.05
	rs4259701	3.3 yrs	GA/AA	GG	Cumulative incidence	P for interaction > 0.05
	rs8138102	3.3 yrs	AG/GG	AA	Cumulative incidence	P for interaction > 0.05
	rs4253728	3.3 yrs	GA/AA	GG	Cumulative incidence	P for interaction > 0.05
	rs11090819	3.3 yrs	GA/AA	GG	Cumulative incidence	P for interaction > 0.05
	rs4253778	3.3 yrs	CC	GC/GG	Adjusted OR	Acarbose: 2.28 (0.88 to 5.86)
						Placebo: 1.32 (0.52 to 3.32)
	rs4253778	3.3 yrs	CC	GC/GG	Cumulative incidence	P for interaction > 0.05
HNF4A						
Andrulionyte, 2006 (32)	rs2425637	3.3 yrs	GG, GT, TT		Cumulative incidence	P for interaction = 0.011
	rs2425637	3.3 yrs	TT	GG/GT	Adjusted OR[a]	Acarbose: 1.53 (0.88 to 2.66)
						Placebo 0.48 (0.28 to 0.82)
	rs3818247	3.3 yrs	GG, GT/TT		Cumulative incidence	P for interaction = 0.030
	rs3818247	3.3 yrs	GT/TT	GG	Adjusted OR	Acarbose: 1.70 (1.08 to 2.70)
						Placebo: 0.84 (0.56 to 1.26)
	rs4810424	3.3 yrs	GG, GC/CC		Cumulative incidence	P for interaction > 0.05
	rs2071197	3.3 yrs	GG, GA/AA		Cumulative incidence	P for interaction > 0.05
	rs2071197	3.3 yrs	GA/AA	GG	Adjusted OR	Acarbose: 0.48 (0.26 to 0.87)
						Placebo: 0.86 (0.54 to 1.38)

	rs736824	3.3 yrs	TT, TC, CC		Cumulative incidence	P for interaction > 0.05
	rs1885088	3.3 yrs	GG, GA/AA		Cumulative incidence	
LIPC						
Zacharova, 2005 (33)	rs2070895	3 yrs	GG, AG, AA		Cumulative incidence[a]	Acarbose: GG: 32.7%, GA: 32.6%, AA: 50%
						Placebo: GG: 43.6%, GA: 45.8%, AA: 68.0%
	rs2070895	3 yrs	GA, AA	GG	Adjusted OR	Acarbose: GA: 0.96 (0.58 to 1.58), AA: 1.96 (0.76 to 5.02),
						Placebo: GA: 1.06 (0.68 to 1.66), AA: 2.49 (0.97 to 6.41)
PPARG2						
Andrulionyte, 2004 (34)	rs1801282	3.3 yrs	Pro12Pro	12Ala	Unadjusted OR	Acarbose: 1.50 (0.88 to 2.58)
						Placebo: 1.11 (0.69 to 1.76)
	rs1801282	3.3 yrs			Cumulative incidence	Acarbose: 12Ala: 27.1%, Pro12Pro: 35.8%
						Placebo: 12Ala 44.1%, Pro12Pro: 46.4%
PPARGC1A						
Andrulionyte, 2004 (34)	rs8192673	3.3 yrs			Adjusted OR[a]	Acarbose: 0.73 (0.46 to 1.15)
						Placebo: 1.56 (1.04 to 2.34)
	rs8192673	3.3 yrs			Mean change	Acarbose: 482Ser: -0.67 mmol/l, Gly482Gly: -0.28 mmol/l,
						Placebo: 482Ser: +0.17 mmol/l, Gly482Gly: +0.67 mmol/l

SUPPLEMENTARY DATA

Supplementary Table 11. Prioritized list of design, analysis, and reporting items suggested for future pharmacogenetic studies in diabetes

Design	**Comments/Rationale**
1. Evaluate prior suggestive interactions with biologic plausibility	Need replication of interactions to inform translation efforts
2. Pre-specify interactions	Pre-specify SNP(s) and medication(s) to avoid selective reporting
3. Use experimental design	Assignment of treatment; prospective, standardized data collection
4. Include comparison group	Concurrent
5. Use uniform outcomes and follow up	Need consensus on relevant outcomes and duration to facilitate comparisons between studies, minimize selective reporting of outcomes, and to inform sample size of future studies
Analysis	
6. Address population stratification	Ancestry informative markers, stratification on race, restriction on race, etc.
7. Incorporate method for addressing multiple comparisons	May be reasonable to use P <0.05 in the context of a single interaction that is a “replication”
8. Estimate sample size prior to study	Based on agreed upon primary outcome(s)
Reporting	
9. Pre-specify gene-drug interactions	Provide rationale for evaluation of interaction
10. Provide information on genotyping quality control	Especially important for *de novo* studies; report or provide reference to metrics which should include genotype success rate, evaluation of Hardy Weinberg Proportions, sex concordance
11. Provide information on genotyped and non-genotyped subjects	May be most important for *de novo* studies in which information on the study population is not provided in prior studies

SUPPLEMENTARY DATA

Quality form

General Questions

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)? This does not refer to the parent study. Select one.

Yes; No; NR

2. Was the study sample selected based on availability of genotyping results? Select one.

Yes; No; NR

3. Does the study describe the number of participants who withdrew or were lost to follow-up after the start of the period of observation? Select one.

Yes, complete (could replicate); Yes, partial (could not replicate); No

4. What was the overall percentage of participants who withdrew or were lost to follow-up after the start of the period of observation? Select one.

≥5%; <5%, NR

5. If ≥5% of participants were lost to follow-up, was this differential by comparison group? Select one.

Yes; No; NR

6. Was adherence to study medications reported? Select one.

Yes; No

7. Was an intention-to-treat (ITT) analysis used for the main comparison and adverse events? Select one.

Yes, for main comparison; Yes, for adverse events; Yes, for both main comparison and adverse events; No; NR; n/a

8. Was there ≥10% missing data overall for the association between the pharmacogenetic interaction and the main outcome? Select one.

Yes; No; NR

9. If ≥ 10% missing data (Yes to #8), how were missing data handled (select all that apply)?

Excluded
Last observation carried forward (LOCF)
Multiple Imputation
Other (specify):
Not reported

10. Were controls at risk for the same amount of time as cases (i.e., same potential exposure time)? Select one.

Yes; No; NR; n/a

Genomics-specific Questions

11. Were the associations reported specified a priori? Select one.

Yes; No, designated as exploratory; NR

12. Are methods for genotyping reported (select all that apply)?

Yes
No
Referenced

13. Specify genotyping method: Select one.

DNA array; PCR; Sequenom; Other (specify); NR

14. For studies using genome-wide association study (GWAS) data, was the allele-calling algorithm (e.g., BRLMM, Birdsweet) specified? Select one.

Yes; No; n/a

15. For studies using GWAS data, what was the mean genotype call (success) rate? Select one.

≥95%; <95%; n/a

16. For studies not using GWAS data, was the genotype success rate for each SNP ≥95%? Select one.

Yes; No; NR; n/a

17. What was the duplicate genotyping concordance? Select one.

≥90%; <90%; NR

18. Which of the following data cleaning strategies for genotyping were used in the study (select all that apply)?

Test for Hardy Weinberg Equilibrium
Verification of sex concordance
Verification of race/ethnicity concordance
Not reported
Other (specify):

19. If Hardy-Weinberg Equilibrium (HWE) checked and alleles were not in HWE, how were they handled? Select one.

n/a (HWE not checked); Excluded based on P value; NR; Other (specify)

20. Was the staff performing genotyping masked to outcome? Select one.

Yes; No; NR

21. Were samples randomly scattered across plates (e.g., cases and controls, active drug and placebo)? Select one.

Yes; No; NR; n/a

22. Was the study funded or supported by a pharmaceutical company? Select one.

Yes; No; NR

23. Please comment on any other quality issues if present:

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