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The Pharmacogenetics of Type 2 Diabetes: A Systematic Review

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SYSTEMATIC REVIEW

OBJECTIVE

We performed a systematic review to identify which genetic variants predict response to diabetes medications.

RESEARCH DESIGN AND METHODS

We performed a search of electronic databases (PubMed, EMBASE, and Cochrane Database) and a manual search to identify original, longitudinal studies of the effect of diabetes medications on incident diabetes, HbA_{1c}, fasting glucose, and postprandial glucose in prediabetes or type 2 diabetes by genetic variation. Two investigators reviewed titles, abstracts, and articles independently. Two investigators abstracted data sequentially and evaluated study quality independently. Quality evaluations were based on the Strengthening the Reporting of Genetic Association Studies guidelines and Human Genome Epidemiology Network guidance.

RESULTS

Of 7,279 citations, we included 34 articles (*N* = 10,407) evaluating metformin (*n* = 14), sulfonylureas (*n* = 4), repaglinide (*n* = 8), pioglitazone (*n* = 3), rosiglitazone (*n* = 4), and acarbose (*n* = 4). Studies were not standalone randomized controlled trials, and most evaluated patients with diabetes. Significant medication–gene interactions for glycemic outcomes included *1*) metformin and the *SLC22A1*, *SLC22A2*, *SLC47A1*, *PRKAB2*, *PRKAA2*, *PRKAA1*, and *STK11* loci; *2*) sulfonylureas and the *CYP2C9* and *TCF7L2* loci; *3*) repaglinide and the *KCNJ11*, *SLC30A8*, *NEUROD1/BETA2*, *UCP2*, and *PAX4* loci; *4*) pioglitazone and the *PPARG2* and *PTPRD* loci; *5*) rosiglitazone and the *KCNQ1* and *RBP4* loci; and *5*) acarbose and the *PPARA*, *HNF4A*, *LIPC*, and *PPARGC1A* loci. Data were insufficient for meta-analysis.

CONCLUSIONS

We found evidence of pharmacogenetic interactions for metformin, sulfonylureas, repaglinide, thiazolidinediones, and acarbose consistent with their pharmacokinetics and pharmacodynamics. While high-quality controlled studies with prespecified analyses are still lacking, our results bring the promise of personalized medicine in diabetes one step closer to fruition.

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In 2013, there existed multiple pharmacologic interventions for the prevention and treatment of type 2 diabetes (1). However, all evaluations of known efficacious interventions reveal that some patients respond to treatment while others do not. As recognized by the American Diabetes Association in its 2012 statement on the management of hyperglycemia, care in type 2 diabetes must become more patient-centered (2), and the individualization of diabetes prevention and treatment based on genetic variation has great potential.

Narrative reviews have commented on the promise of pharmacogenomics of type 2 diabetes (3–6), and prominent individual studies have found statistically significant pharmacogenetic interactions associated with diabetes risk and glycemic outcomes (7–11). However, prior reviews have not systematically evaluated this literature to inform future research questions, and these reviews do not address the quality issues that affect the existing literature on diabetes pharmacogenetics. The clinical utility of genetic variation for tailoring diabetes medications rests on the identification of substantial and statistically significant pharmacogenetic interactions from internally valid studies and confirmation of their findings in varied populations based on race/ethnicity.

We conducted a systematic review of observational and experimental studies to determine if the effect of diabetes medications on diabetes incidence, HbA_{1c}, fasting glucose (FG), and postprandial glucose (PPG) varies by independent genetic variation in patients with impaired FG, impaired glucose tolerance, or type 2 diabetes. We hypothesized that *1*) genetic variation associated with drug transporters, metabolizers, targets, and mechanisms of action would modify the effect of specific drugs and *2*) the existing evidence would be insufficient to recommend clinical use of pharmacogenetic interactions because of a lack of well-conducted studies across diverse populations.

RESEARCH DESIGN AND METHODS

Senior members of the study were diabetes and obesity researchers with training in clinical epidemiology, clinical trials, and systematic review methodology (E.B., W.L.B., J.M.C., S.B., W.H.L.K., N.M.M., and M.O.G.) and genetic epidemiology (P.B., W.H.L.K., N.M.M., and M.O.G.). The team also included an experienced project manager with expertise in the conduct of systematic reviews (L.M.W.).

We searched the PubMed, EMBASE, Cochrane electronic databases and also manually searched key review articles, key journals' tables of contents, and the references of included articles. Key journals were selected based on content area and ones that commonly published the included articles. The PubMed search and list of key journals are provided in Supplementary Tables 1 and 2. The electronic search included dates of database inception through 13 March 2013, and the manual search of tables of contents included January to March 2013. The search was limited to studies published in English.

We included original articles on the effect of Food and Drug Administration (FDA)-approved diabetes medications (Supplementary Table 3) on diabetes incidence, HbA_{1c}, FG, and PPG in adults with either type 2 diabetes or increased diabetes risk because of impaired FG (FG 5.55–6.94 mmol/L) or impaired glucose tolerance (2-h postload [75 g] glucose 7.77–11.04 mmol/L) by common genetic variation. We considered any independent genetic variation (e.g., single nucleotide polymorphisms [SNPs], copy number variants) eligible and excluded variation such as haplotypes. Eligible study designs were *1*) controlled studies evaluating the effect of a drug for one allele/genotype versus another over time and *2*) uncontrolled studies evaluating the effect (change in outcome or incidence of outcome) of a drug comparing one genotype/allele to another. We excluded studies of less than 24-h duration and did not include results for HbA_{1c} in studies shorter than 3 months.

We excluded case reports, case series, and cross-sectional studies; studies not written in English (due to lack of availability of resources to interpret these articles); and studies that included participants on more than one diabetes medication. We did not contact authors to obtain additional results from included studies.

Two investigators reviewed each title, abstract, and full-text article independently. A citation was advanced to abstract review if a single investigator included it. Abstracts and full-text articles were reviewed using a standardized and piloted eligibility criteria form, and disagreements were resolved through consensus.

We developed data abstraction forms based on included abstracts and articles. Data abstraction forms were piloted extensively and included information on study design, study population characteristics, genetic variation under study, and study results on outcomes of interest. Abstraction forms were completed using DistillerSR online systematic review management software. Two investigators abstracted data sequentially using the finalized standardized forms.

We developed quality abstraction forms based on the Strengthening the Reporting of Genetic Association Studies guidelines for reporting of genetic association studies (12). In the absence of guidelines for pharmacogenetic studies, we also incorporated recommendations from the HuGENet (Human Genome Epidemiology Network) HuGE Review Handbook (13) and prior methodological papers (14). We considered a study to be randomized if it randomized participants for the pharmacogenetic study and was not simply based on a prior randomized study. Forms captured elements of quality control of genotyping, including method of genotyping and genotyping call rate, and we considered a call rate $\geq$95% to be acceptable. We calculated genotype call rates when possible. We also recorded genotyping concordance as a genotyping quality metric. We considered selective reporting of interactions based on positive results and selection bias related to availability of genotyping (Supplementary Data). Two investigators evaluated the quality of each study independently, and disagreements were resolved through consensus.

We performed a qualitative synthesis of included studies' results. We were unable to perform quantitative syntheses with meta-analyses because too few studies contained the same SNP–drug interactions with common outcomes.

Funding sources had no role in the design, conduct, analysis, or interpretation of the study.

RESULTS

Of 7,279 citations, we included 34 articles from 21 studies (7,8,10,15–45) comprised of 10,407 subjects (Fig. 1). The included articles used one of three study designs: *1*) subanalysis of prior randomized controlled trials (RCTs; *n* = 13); *2*) analysis of observational data (*n* = 8); and *3*) nonrandomized, experimental, pre–post design without a control group (*n* = 13) (Table 1). None of the studies were de novo RCTs specifically designed to evaluate pharmacogenetic interactions. With the exception of the Stop Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) trial (20–23) and the Diabetes Prevention Program (DPP) (7,8,17–19,36,37,45), all studies evaluated pharmacogenetic interactions in patients with diabetes. In the DPP, a randomized trial of metformin, a lifestyle intervention, and placebo for diabetes prevention, a broad candidate gene approach (more than 1,590 candidate gene loci) was taken to evaluate associations of SNPs with diabetes and interactions between genetic variants and the trial's interventions (1 to 3.2 years of follow-up) (7,8,17–19,36,37,45). Genetics of Diabetes Audit and Research Tayside (GoDARTS) investigators performed retrospective analyses of observational data from patients with diabetes who had 12 to 18 months of follow-up using both a genome-wide (10) and candidate gene approach (15,16). The ethnic composition of each study is provided in Table 1. No study evaluated interactions for the other

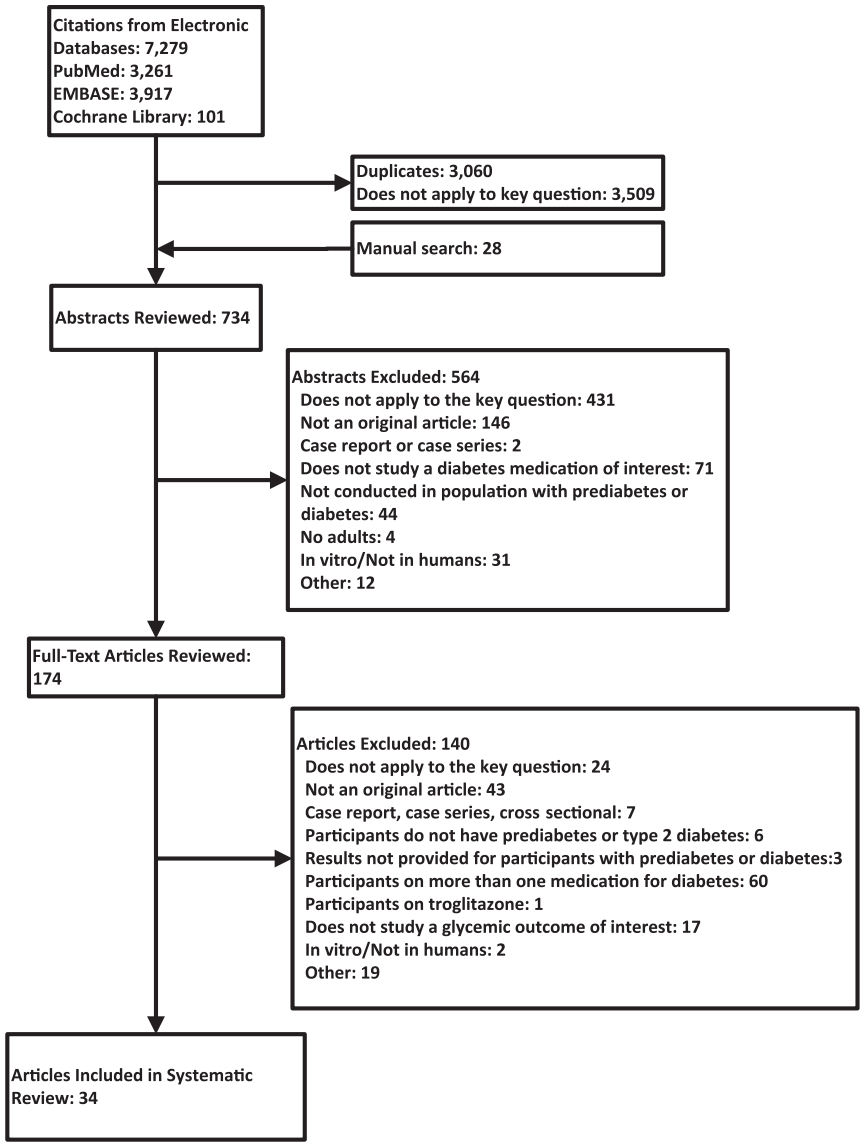

Figure 1—Selection of included studies.

Table 1—Description of included studies

First author	Parent study	Study design	Diabetes status	Comparator	Gene	*N*	Ethnicity*
Metformin							
Choi, 2011 (34)	SOPHIE	Observational	Diabetes	None	*MATE2-K*†	253	Multiethnic
Dong, 2011 (35)	NA	Experimental	Diabetes	None	*SRR*	44	Chinese
Florez, 2006 (17)	DPP	Experimental	Prediabetes	Placebo	*TCF7L2*	3,548	Multiethnic
Florez, 2008 (19)	DPP	Experimental	Prediabetes	Placebo	*WFS1*	3,548	Multiethnic
Florez, 2007 (18)	DPP	Experimental	Prediabetes	Placebo	*KCNJ11*	3,547	Multiethnic
Florez, 2012 (36)	DPP	Experimental	Prediabetes	Placebo	‡	2,890	Multiethnic
Florez, 2012 (37)	DPP	Experimental	Prediabetes	Placebo	*ATM*	2,984	Multiethnic
Moore, 2008 (9)	DPP	Experimental	Prediabetes	Placebo	§	3,548	Multiethnic
Moore, 2009 (8)	DPP	Experimental	Prediabetes	Placebo	*ENPP1*	3,548	Multiethnic
Jablonski, 2010 (7)	DPP	Experimental	Prediabetes	Placebo	**	2,294	Multiethnic
Pearson, 2007 (15)	GoDARTS	Observational	Diabetes	None	*TCF7L2*	945	NR
Tkáč, 2013 (38)	NA	Experimental	Diabetes	None	*SLC47A1*, *SLC22A1*, *SLC22A2*	148	Caucasian
Zhou, 2009 (16)	GoDARTS	Observational	Diabetes	None	*SLC22A1*	1,014	NR
Zhou, 2011 (10)	GoDARTS	Observational	Diabetes	None	††	3,540	NR
Sulfonylureas							
Suzuki, 2006 (25)	NA	Experimental	Diabetes	None	*CYP2C9*	134	Asian
Gloyn, 2001 (24)	UKPDS	Experimental	Diabetes	None	*KCNJ11*	364	White
Pearson, 2007 (15)	GoDARTS	Observational	Diabetes	None	*TCF7L2*	901	NR
Becker, 2008 (26)	Rotterdam Study	Observational	Diabetes	None	*CYP2C9*	475	White
Repaglinide							
Gong, 2012 (39)	NA	Experimental	Diabetes	None	*PAX4*, *NEUROD1/BETA2*	43	Chinese
He, 2008 (27)	NA‡‡	Experimental	Diabetes	None	*KCNJ11*	100	Asian§§
Huang, 2010 (28)	NA	Experimental	Diabetes	None	*SLC30A8*	48	Chinese
Jiang, 2012 (40)	NA	Experimental	Diabetes	None	*SLC30A8*	209	Chinese
Sheng, 2011 (41)	NA	Experimental	Diabetes	None	*NAMPT*	35	Chinese
Qin, 2010 (29)	NA	Observational	Diabetes	None	*NOS1AP*	100	Asian
Wang, 2012 (44)	NA	Experimental	Diabetes	None	*UCP2*	41	Chinese
Yu, 2011 (30)	NA‡‡	Experimental	Diabetes	None	*KCNQ1*	91	Asian
Pioglitazone							
Blüher, 2003 (32)	NA	Experimental	Diabetes	None	*PPARG2*	131	NR
Pei, 2013 (42)	NA	Experimental	Diabetes	None	*PPARG2*, *PTPRD*	67	Chinese
Saitou, 2010 (33)	NA	Observational	Diabetes	Diet	*ACE*	222	Asian**
Rosiglitazone							
Jiang, 2012 (40)	NA	Experimental	Diabetes	None	*SLC30A8*	209	Chinese
Wang, 2008 (31)	NA	Experimental	Diabetes	None	*ABCA1*	93	Asian**
Yu, 2011 (30)	NA‡‡	Experimental	Diabetes	None	*KCNQ1*	91	Asian
Zhou, 2011 (43)	Unclear	Experimental	Diabetes	None	*RBP4*	42	Chinese
Acarbose							
Andrulionyte, 2004 (22)	STOP-NIDDM	Experimental	Prediabetes	Placebo	*PPARG2*	770	White***
Andrulionyte, 2007 (20)	STOP-NIDDM	Experimental	Prediabetes	Placebo	*PPARA*	767	White***
Andrulionyte, 2006 (21)	STOP-NIDDM	Experimental	Prediabetes	Placebo	*HNF4A*	769	White***
Zacharova, 2005 (23)	STOP-NIDDM	Experimental	Prediabetes	Placebo	*LIPC*	770	98% White

NA, not applicable; NR, not reported; SOPHIE, Study Of Pharmacogenetics In Ethnically diverse populations; UKPDS, UK Prospective Diabetes Study. *If only one ethnicity reported, the prevalence of that ethnicity is 100% in the study population. †This study also evaluated SNPs in *OCT1*, *OCT2*, and *MATE1*. ‡The study evaluated SNPs from the following loci: *G6PC2*, *MTNR1B*, *GCK*, *DGKB*, *GCKR*, *ADCY5*, *MADD*, *CRY2*, *ADRA2A*, *FADS1*, *PROX1*, *SLC2A2*, *GLIS3*, *C2CD4B*, *IGF1*, and *IRS1*. §The study evaluated SNPs from the following loci: *CDKN2A/B*, *EXT2*, *CDKAL1*, *IGF2BP2*, *HHEX*, *LOC387761*, and *SLC30A8*. **The study evaluated 1,590 SNPs. ††The study conducted a genome-wide association study and genotyped 705,125 SNPs from the Affymetrix 6.0 microarray. ‡‡He et al. (27) and Yu et al. (30) are based on the same study population. §§Assumed based on location of study (China, Korea, Japan). ***Assumed based on reported results in Zacharova et al. (23) since from same study.

included FDA-approved medications of interest.

Metformin

Genetic interactions with metformin were reported in 14 articles (Table 2; Supplementary Table 4) (7,8,10,15–19,34–38,45).

Genes encoding the metformin transporters, *SLC22A1*, *SLC22A2*, and *SLC47A1*, were each studied in four articles that evaluated different outcomes. For the *SLC22A1* locus, rs683369 was associated with response to metformin with respect to diabetes risk in the DPP over 3.2 years (7), and three SNPs were not associated with HbA_{1c} in people with diabetes in two other studies (16,38). For *SLC22A2*, rs662301 was associated with risk of diabetes at 3.2 years in the metformin arm versus placebo in the DPP (7), and two SNPs were not associated with response to metformin with FG and

Table 2—Interaction between metformin and selected SNPs for glycemic outcomes

			SNPs with significant interactions/SNPs studied for outcome†		
Putative function	Gene	SNPs*	Diabetes risk	HbA_{1c}	FG
Metformin transporters					
	SLC22A1	rs4646281 (16), rs12208357 (16), rs683369 (7), rs622342 (38)	1/1	0/3	NA
	SLC22A2	rs662301 (7), rs11920090 (36), rs316019 (34,38)	1/1	0/1‡	0/1
	SLC47A1	rs8065082 (7), rs2289669 (34,38)	1/1	0/1§	NA
AMP-activated protein kinase pathway/gluconeogenesis					
	PRKAA1	rs249429 (7)	1/1	NA	NA
	PRKAB2	rs6690158 (7)	1/1	NA	NA
	PRKAA2	rs9803799 (7)	1/1	NA	NA
	ATM	rs11212617 (10)**(37)††	1/1	0/1‡‡	0/1
	STK11	rs741765 (7)	1/1	NA	NA
	PPARA	rs4253652 (7)	1/1	NA	NA
	PPARGC1A	rs10213440 (7)	1/1	NA	NA
	PCK1	rs4810083 (7)	1/1	NA	NA
Insulin secretion					
	KCNJ11	rs5219 (E23K) (18), rs7124355 (7)	1/2	NA	NA
	ABCC8	rs4148609 (7)	1/1	NA	NA
	TCF7L2	rs12255372 (15,17), rs7903146 (15,17)	0/2	0/2	NA
	WFS1	rs734312, rs10010131, rs752854 (19)	0/3	NA	NA
	CDKN2A/B	rs10811661 (45)§§	1/1	NA	NA
	HNF4A	rs11086926 (7)	1/1	NA	NA
	HNF1B	rs11868513 (7)	1/1	NA	NA
	GLIS3	rs7034200 (36)	NA	NA	0/1
	G6PC2	rs573225 (36)	NA	NA	0/1
	MADD	rs7944584 (36)	NA	NA	1/1
	MTNR1B	rs10830963 (36)	NA	NA	0/1
	ADCY5	rs11708067 (36)	NA	NA	0/1
Insulin sensitivity					
	ADIPOR2	rs758027 (7)	1/1	NA	NA
	ENPP1	rs1044498 (8)	1/1	NA	NA
	CAPN10	rs3792269 (7)	1/1	NA	NA
	GCK	rs2908289 (7), rs917793 (36)	1/1	NA	0/1
	IRS1	rs4675095 (36)	NA	NA	0/1
	IGF1	rs855228 (36)	NA	NA	0/1
	GCKR	rs780094 (36)	NA	NA	0/1
Energy metabolism					
	MEF2A	rs424892 (7)	1/1	NA	NA
	MEF2D	rs6666307 (7)	1/1	NA	NA
	CRY2	rs11605924 (36)	NA	NA	0/1
Other					
	ITLN2	rs6701920 (7)	1/1	NA	NA
	GCG	rs6733736 (7)	1/1	NA	NA
	PKLR	rs17367421 (7)	1/1	NA	NA
	PPARGC1B	rs741579 (7)	1/1	NA	NA
	SRR	rs391300 (35)	NA	0/1	1/1***
	PROX1	rs340874 (36)	NA	NA	0/1
	DGKB	rs2191349 (36)	NA	NA	0/1
	ADRA2A	rs10885122 (36)	NA	NA	0/1
	FADS1	rs174550 (36)	NA	NA	0/1
	C2CD4B	rs11071657 (36)	NA	NA	1/1

NA, not applicable. *Jablonski et al. (7) explored a total of 1,590 candidate SNPs. Results for 24 loci for which the *P* for interaction was < 0.05 are presented. In total, 91 SNPs demonstrated a significant interaction with metformin, and the 24 SNPs reported here represent the loci for these 91 SNPs. †Number of SNPs with significant interaction ($P < 0.05$) out of the total number of SNPs studied at the locus. ‡rs316019 was evaluated for interaction effect on HbA_{1c} in two studies. §rs2289669 was evaluated for interaction effect on HbA_{1c} in two studies. **This study was a genome-wide association study and genotyped 705,125 SNPs using the Affymetrix 6.0 microarray. ††rs11212617 was evaluated in two studies. ‡‡Two studies evaluated the interaction between rs11212617 and metformin with HbA_{1c} as an outcome. §§This study explored 10 other candidate SNPs for which the interaction between the genetic variant and treatment was not significant in the following loci: *EXT2*, *CDKAL1*, *IGF2BP2*, *HHEX*, *LOC387761*, and *SLC30A8*. ***$P = 0.048$ for 2-h PPG.

HbA_{1c} as outcomes in three other articles (34,36,38). For the *SLC47A1* locus, rs8065082 was associated with response to metformin for diabetes risk (7), and rs2289669 was not associated with metformin response in patients with diabetes (HbA_{1c} as the outcome) (34,38).

rs11212617 at the *ATM* locus predicted response to metformin for diabetes risk at 1 year in the DPP (37) and attainment of HbA_{1c} <7% (53 mmol/mol) at 18 months in GoDARTS (10). However, results for HbA_{1c} and FG at 1 year were not significant in the DPP (37). Neither GoDARTS or the DPP found a significant interaction for *TCF7L2* SNPs for attainment of HbA_{1c} <7% (53 mmol/mol) (15) or diabetes incidence (17).

Statistically significant interactions between metformin and genetic variants were also reported for genes encoding additional proteins associated with AMP-activated protein kinase–dependent inhibition of gluconeogenesis [*PRKAB2*, *PRKAA2*, *PRKAA1*, *STK11* (46,47), *PCK1*, *PPARA* (48), and *PPARGC1A* (7,49)], insulin secretion [*KCNJ11* (7,18), *ABCC8*, *CDKN2A/B* (45), *HNF4A*, and *HNF1B* (7)]; and insulin sensitivity [*ADIPOR2*, *ENPP1* (8), *CAPN10*, and *GCK* (7)] (Table 2; Supplementary Table 4).

Sulfonylureas

Four studies evaluated the interaction between sulfonylureas and SNPs (Table 3; Supplementary Table 5) (15,24–26). Of two studies evaluating SNPs in *CYP2C9* (25,26), the gene encoding the primary hepatic cytochrome P450 enzyme, which metabolizes sulfonylureas, one small study found a greater mean change from baseline in HbA_{1c} at 6 months by diplotype of rs1057910 (25). Notably, the sample size for the variant diplotype was very small (n = 2) (25).

Table 3—Interaction between sulfonylureas, repaglinide, thiazolidinediones, and acarbose and selected SNPs for glycemic outcomes

		SNPs with significant interactions/SNPs studied for outcome*			
Gene	SNPs	Diabetes	HbA_{1c}	FG	PPG†
Sulfonylureas					
TCF7L2	rs79031462, rs12255372 (15)	NA	2/2	NA	NA
KCNJ11	rs5219 (E23 K), rs1800467 (24)	NA	NA	0/2	NA
CYP2C9‡	rs1057910 (25,26), rs1799853 (26)	NA	1/1	0/2	NA
Repaglinide					
KCNJ11	rs5219 (27)	NA	1/1	0/1	1/1
ABCC8	rs1799854 (27)	NA	0/1	0/1	0/1
KCNQ1	rs2237892, rs2237895, rs2237897 (30)	NA	0/3	0/3	0/3
SLC30A8	rs13266634 (28,40),§ rs16889462 (28)	NA	1/2	1/2	1/2
NOS1AP	rs10494366 (29)	NA	0/1	0/1	0/1
NEUROD1/BETA2	A45T (39)	NA	0/1	1/1	1/1
PAX4	R121 W (39)	NA	0/1	0/1	1/1
NAMPT	−3186C/T (41)	NA	0/1	0/1	0/1
UCP2	rs659366 (44)	NA	1/1	1/1	0/1
Pioglitazone					
PPARG2	rs1801282 (Pro12Ala) (32,42)**	NA	0/1	1/1	0/1
ACE	rs1799752 (33)	NA	0/1	NA	NA
MTHFR	rs1801133 (33)	NA	0/1	NA	NA
PTPRD	rs17584499 (42)	NA	0/1	0/1	1/1
Rosiglitazone					
ABCA1	rs2230806, rs4149313, rs2230808 (31)	NA	0/3	0/3	0/3
KCNQ1	rs2237892, rs2237895, rs2237897 (30)	NA	0/3	0/3	1/3
SLC30A8	rs13266634 (40)	NA	0/1	0/1	0/1
RBP4	rs3758539, rs10882283 (43)	NA	1/2	1/2	0/2
Acarbose					
PPARA	rs1800206, rs4253776, rs4253623, rs135547, rs135542, rs135539, rs4259701, rs8138102, rs4253728, rs11090819, rs4253778 (20)	2/11	NA	NA	NA
HNF4A	rs2425637, rs3818247, rs4810424, rs2071197, rs736824, rs1885088 (21)	2/6	NA	NA	NA
LIPC	rs2070895 (23)	1/1	NA	NA	NA
PPARG2	rs1801282 (22)	0/1	NA	NA	NA
PPARGC1A	rs8192673 (22)	1/1	NA	NA	NA

NA, not applicable. *Number of SNPs with significant interaction ($P < 0.05$) out of the total number of SNPs studied at the locus. †PPG is the 2-h glucose result from oral glucose tolerance test. ‡By convention, for *CYP2C9*, numerals (e.g., 1, 2, and 3) are used to identify haplotypes rather than base or amino acid changes, and the "1" allele is the wild-type or ancestral haplotype (technically, "1A"; The Human Cytochrome P450 Allele Nomenclature Committee; *CYP2C9* allele nomenclature; http://www.cypalleles.ki.se/cyp2c9.htm, accessed 5 November 2013). §Two studies evaluated rs13266634 for an interaction with HbA_{1c}, FG, and PPG, with one of these finding a significant interaction for each outcome. **Two studies evaluated the Pro12Ala variant for an interaction with HbA_1, FG, and HbA_{1c}; a single study found a significant interaction for FG.

GoDARTS evaluated the interaction between two *TCF7L2* SNPs and sulfonylureas and reported a significant association with response to medication (15). Another study evaluating the interaction between two *KCNJ11* SNPs and sulfonylureas did not find any differences in the change in FG across genotypes at 12 months (24).

Repaglinide

Eight articles reported on genetic interactions with repaglinide (Table 3; Supplementary Table 6) (27–30,39–41,44). Of two SNPs evaluated in the *SLC30A8* gene (28,40), rs13266634 was associated with response to repaglinide using HbA_{1c}, FG, and PPG at 8 weeks as outcomes (28). Similar, but nonsignificant, results were observed with the other SNP evaluated (D′ = 0.928 for rs168889462 and rs13266634) (28). Notably, rs13266634 has been one of the most replicated genetic risk variants in type 2 diabetes (50).

A single study reported a significantly different change in HbA_{1c} and PPG at 6 months (and similar, nonsignificant results for FG) by E23K genotype of *KCNJ11*, which encodes the potassium channel inhibited by binding of repaglinide to its receptor on the β-cell (27). SNPs in *NEUROD1/BETA2*, *PAX4* (39), and *UPC*2 (44) predicted response to repaglinide for some glycemic outcomes (Table 3).

Pioglitazone

Three studies reported on interactions between pioglitazone and genetic variation (32,33,42) (Table 3; Supplementary Table 7). The Pro12Ala variant was associated with pioglitazone response in one (42) of two studies evaluating this SNP (32,42). A single study reported a significant effect of *PTPRD* rs17584499 genotype on PPG at 12 weeks but not on HbA_{1c} or FG (42).

Rosiglitazone

Four studies reported on response to rosiglitazone by genetic variation (Table 3; Supplementary Table 8) (30,31,40,43). Individual studies reported significant interactions between the *KCNQ1* (30) and *RBP4* (43) loci and rosiglitazone for some, but not all, glycemic measures.

Acarbose

Interactions between acarbose and the *PPARA*, *HNF4A*, *LIPC*, *PPARG2*, and *PPARGC1A* loci were evaluated in the STOP-NIDDM trial with 3.3 years of follow-up for diabetes risk (Table 3; Supplementary Table 9) (20–23). Two of 11 SNPs from the *PPARA* locus were associated with response to acarbose (20). Of six SNPs from the *HNF4A* locus, two were associated with response to acarbose (21). Single SNPs at the *LIPC* and the *PPARGC1A* loci were also associated with response to acarbose (22,23).

Quality of Included Studies

We provide detailed results on the quality of included studies in Supplementary Table 10. None of the included studies was a prospective RCT designed to evaluate a pharmacogenetic interaction, and only 13 of 34 (38%) had a control group. Twenty-six of 34 (76%) studies did not report on losses to follow-up. Pharmacogenetic analyses were prespecified in 24 of 34 (71%) studies and were either not reported or not prespecified in the remainder of the studies. Sixteen of 34 (47%) studies addressed the issue of multiple comparisons (or only looked at a single SNP). Thirty-one of 34 studies (91%) addressed population stratification by adjusting for admixture or self-reported race/ethnicity or only included one race/ethnicity. All studies provided some information on method of genotyping. Only 14 of 34 (41%) reported on genotyping or SNP-specific call rate. Most studies (24 of 34 [71%]) did not report on genotyping concordance. Twenty-seven of 34 (79%) reported on testing for Hardy–Weinberg proportions. Studies did not report on masking of genotyping personnel, and 41% declared some form of industry support.

CONCLUSIONS

In this systematic review, we identified 34 articles on the pharmacogenetics of diabetes medications, with several reporting statistically significant interactions between genetic variants and medications for glycemic outcomes. Most pharmacogenetic interactions were only evaluated in a single study, did not use a control group, and/or did not report enough information to judge internal validity. However, our results do suggest specific, biologically plausible, gene–medication interactions, and we recommend confirmation of the biologically plausible interactions as a priority, including those for drug transporters, metabolizers, and targets of action. In particular, we recommend follow-up of the *1*) *SLC22A1*, *SLC22A2*, *SLC47A1*, *PRKAB2*, *PRKAA2*, *PRKAA1*, and *STK11* loci for metformin; *2*) *CYP2C9* and *TCF7L2* loci for sulfonylureas; *3*) *KCNJ11*, *SLC30A8*, *NEUROD1/BETA2*, *UCP2*, and *PAX4* loci for repaglinide; *4*) *PPARG2* and *PTPRD* for pioglitazone; *5*) *KCNQ1* and *RBP4* loci for rosiglitazone; and *6*) *PPARA*, *HNF4A*, *LIPC*, and *PPARGC1A* loci for acarbose.

Given the number of comparisons reported in the included studies and the lack of accounting for multiple comparisons in approximately 53% of studies, many of the reported findings may be false positives. However, we expect interactions between response to medications and genes encoding their transporters, metabolizers, targets, and components of their pathways for action as observed in the included studies. The DPP reported significant interactions between metformin and loci for its transporters (*SLC22A1*, *SLC22A2*, and *SLC47A1*) (7). It deserves mention that positive findings were not replicated in other studies evaluating these loci (16,34,38), but outcomes (mean change in quantitative traits, achievement of $HbA_{1c} < 7\%$ (53 mmol/mol) versus diabetes risk in the DPP) and follow-up time (6 to 18 months vs. 3 years in the DPP) differed in the other studies as well as did study design. The DPP also reported on significant interactions for loci associated with metformin pharmacodynamics (*PRKAB2*, *PRKAA2*, *PRKAA1*, and *STK11)* (7,46). The primary action of metformin is the inhibition of hepatic glucose production through inhibition of gluconeogenesis, and interactions with loci associated within this pathway (*PCK1*, *PPARA*, and *PPARGC1A*) were reported (7,48,49). Sulfonylureas and repaglinide bind to the sulfonylurea receptor (encoded by *ABCC8*), which

then inhibits the function of the potassium channel encoded by *KCNJ11* and causes β-cell depolarization and eventual insulin secretion. While we did identify interactions between repaglinide and *KCNJ11* (27), this locus was not associated with sulfonylurea action in a single study that evaluated FG (24). Variation in *CYP2C9*, which encodes an enzyme that metabolizes sulfonylureas, was associated with response to sulfonylureas in one (25) of two studies (25,26). Finally, the thiazolidinediones activate peroxisome proliferator-activated receptor γ receptors, which regulate expression of genes important for sensitivity to insulin. Thus, variation in *PPARG* would likely affect response to this class of medications, and this was suggested in one (42) of the two studies (32,42) evaluating this for pioglitazone and was not evaluated for rosiglitazone.

Many putative loci were not evaluated in the included studies. Variation in the hepatic cytochrome P450 enzymes, which metabolize diabetes medications, would be expected to impact their effects, including variation in *CYP3A4* and *CYP2C8* for repaglinide (51), *CYP2C8* and *CYP2C9* for rosiglitazone (52), and *CYP2C8* and *CYP3A4* for pioglitazone (53). The transporter encoded by *SLCOB1* transports repaglinide into hepatocytes for metabolism, and variation in this gene could affect the response to this medication (51). Acarbose primarily decreases intestinal glucose absorption by inhibiting brush border enzymes that hydrolyze carbohydrates and is mainly excreted fecally and does not seem to have obvious pharmacokinetic or pharmacodynamic targets.

Generally, we would also expect genetic variants that impact β-cell function to affect the response to insulin secretagogues and genetic variants that impact insulin sensitivity to affect response to insulin sensitizing medications. Also, because of its primary effect on PPG, genetic variation impacting glucose-stimulated insulin secretion would likely impact the response to acarbose. This rationale may explain other observed significant pharmacogenetic interactions (e.g., rosiglitazone–*KCNQ1*, repaglinide–*SLC30A8*, sulfonylurea–*TCF7L2*, and acarbose–*HNF4A*).

Prior work in this area has consisted of mainly narrative reviews, many of which have included the studies that we identified (3–6). We add to this literature by using a thorough and systematic approach with double review at all levels to identify as many studies as possible that have reported some interaction between individual diabetes medications of interest and diabetes risk and glycemic outcomes. Thus we present the state of the literature on the pharmacogenetics of type 2 diabetes, which lays the groundwork for directing future research efforts. Another novel contribution of our systematic review is the collection of detailed quality information from included studies, which aids in the interpretation of prior studies and illuminates areas for improvement and standardization.

The major limitation of the literature on the pharmacogenomics of type 2 diabetes is the lack of high-quality studies to identify and confirm findings for specific drug–SNP–outcome combinations: *1*) The rationale for selection of loci and interactions studied was often not clear, which raises the concern of selective reporting of results and publication bias; in particular, we would be less suspicious of false-positive results in the setting of prespecified analyses based on prior evidence and/or biologic plausibility with adjustment for multiple comparisons. Therefore, it is likely that positive results were reported and that null results were not. *2*) The small size of many of the studies does not exclude the possibility that interactions exist but could not be identified because of lack of power; we reported study results as significant based on a *P* value less than 0.05 but have noted results when *P* values were <0.20 when possible. Meta-analysis could help to address this issue, but the heterogeneity of studies with specific SNP–drug interactions, outcomes, and follow-up times differing across studies precluded quantitative synthesis with meta-analyses. While our qualitative synthesis summarizes the literature and suggests the existence of specific gene–drug interactions, we could not complete meta-analyses to quantify these observations. *3*) Most studies did not have a placebo or other control group. Therefore, our inferences often relied on the results of a single medication intervention on change in or incidence of outcomes by genotype; these types of studies do not exclude the possibility that we are simply observing the effect of genotype and not specifically modification of the response to the medication. *4*) Studies did not generally provide information to determine the potential for selection bias based on availability of genotyping information, on losses to follow up, or on the amount and handling of missing data. Regarding selection bias due to availability of genotyping, participant behaviors (e.g., adherence to intervention, follow-up) and outcomes (diabetes, death) may have differed between those with and without genotyping information; these kinds of differentiating characteristics in participants included in genetic analyses could impact the observed gene–drug interactions. *5*) While studies did provide information on methods for genotyping, information on SNP-specific call rate was often not reported, and studies did not report on masking of personnel performing genotyping. *6*) While none of the included studies were actually de novo RCTs, which would limit selection bias and confounding most completely, several articles were based on data from prior, well-conducted randomized trials (7,8,17–23,36,37,45). In the case of these trials, we would not expect that participant characteristics correlated with genotype would be related to assigned intervention and thus can feel more confident about the robustness of these studies. To address these issues with quality, we did tailor our inclusion criteria and abstraction tools to limit the inclusion of poor-quality studies and to understand the important potential sources of bias.

One limitation of our systematic review methodology is the exclusion of studies of patients on more than one diabetes medication. We sought to identify pharmacogenetic interactions that were based on a single drug and single genetic variant and wanted to avoid drug–drug–SNP interactions. Future work could

address these types of interactions. Because of this exclusion, we did not include additional articles on the pharmacogenetics of diabetes in this review (11,54–56). These studies did report positive findings regarding gene–drug interactions based on pharmacodynamics [e.g., *PPARG*–rosiglitazone (54), *SLC22A1*–metformin (11), *IRS1*–sulfonylurea (55), and *ATM*–metformin (56)]. These studies confirm our hypotheses regarding the possibility of gene–drug interactions based on pharmacodynamics but are still individual studies different enough from the existing literature to preclude meta-analysis. We also excluded studies of non-FDA-approved medications and therefore did not include the article by Feng et al. evaluating interactions with gliclazide; this study did demonstrate a significant interaction between gliclazide and *ABCC8* and *KCNJ11* SNPs consistent with the pharmacodynamics of sulfonylureas (57). We limited our analyses to diabetes and glycemic outcomes (HbA_{1c}, FG, PPG) because these are more commonly and consistently measured and are also strongly associated with improvements in long-term complications and mortality (58). Future studies should evaluate other important efficacy and safety outcomes. Finally, because of study resource limitations, we excluded non-English language studies from our initial search and cannot estimate the number of otherwise-eligible studies that we excluded based on this.

Guidance for the Development of Future Evidence in Diabetes Pharmacogenetics

We recommend that guidelines for the design, analysis, and reporting of pharmacogenetic studies of diabetes medications be developed to improve study quality and enhance comparability among studies; we have provided a prioritized list of quality and reporting items in Supplementary Table 11. The incorporation of response to medications based on genetic variation into clinical practice cannot occur without well-designed studies confirming significant pharmacogenetic interactions. Based on the limitations of the current literature, we recommend the following for future studies: *1*) a priori specification of the SNPs and medications to be studied, *2*) the use of experimental designs, *3*) inclusion of a concurrent comparison group when possible, *4*) agreement in the diabetes pharmacogenetics community regarding standardized outcomes and follow-up (e.g., HbA_{1c} at 3 months), *5*) sufficient power for the primary outcome, *6*) adjustment for multiple comparisons if multiple SNPs are examined, and *7*) controlling for population stratification and relatedness. In addition, independent replication is important. We recommend that diabetes pharmacogenetics studies use current guidelines for reporting of genetic association studies (12) and that these guidelines be extended to emphasize information relevant to pharmacogenetic studies, including prespecified reporting of analyses with rationale, estimates of type 2 error, standardized reporting of medication interventions, and reporting of differences between genotyped and nongenotyped subjects when possible.

In conclusion, for all known efficacious diabetes preventive and therapeutic pharmacologic agents, some patients benefit or experience harm while others do not. In this systematic review, we find evidence of biologically plausible pharmacogenetic interactions for metformin, sulfonylureas, repaglinide, pioglitazone, rosiglitazone, and acarbose, but these results require confirmation in future studies to determine if an individual's genetic information can be used to individualize the choice of prediabetes and diabetes pharmacologic management. Importantly, our results should guide the development of guidelines for the design, conduct, and reporting of studies of the pharmacogenetics of type 2 diabetes and other chronic conditions. These promising results show the potential of using genetic variation to tailor therapy for type 2 diabetes prevention and management.

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