

REVIEW ARTICLE

Pharmacogenetics of type 2 diabetes mellitus, the route toward tailored medicine

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Summary

Type 2 diabetes mellitus (T2DM) is a chronic disease that has reached the levels of a global epidemic. In order to achieve optimal glucose control, it is often necessary to rely on combination therapy of multiple drugs or insulin because uncontrolled glucose levels result in T2DM progression and enhanced risk of complications and mortality. Several antihyperglycemic agents have been developed over time, and T2DM pharmacotherapy should be prescribed based on suitability for the individual patient's characteristics. Pharmacogenetics is the branch of genetics that investigates how our genome influences individual responses to drugs, therapeutic outcomes, and incidence of adverse effects. In this review, we evaluated the pharmacogenetic evidences currently available in the literature, and we identified the top informative genetic variants associated with response to the most common anti-diabetic drugs: metformin, DPP-4 inhibitors/GLP1R agonists, thiazolidinediones, and sulfonylureas/meglitinides. Overall, we found 40 polymorphisms for each drug class in a total of 71 loci, and we examined the possibility of encouraging genetic screening of these variants/loci in order to critically implement decision-making about the therapeutic approach through precision medicine strategies. It is possible then to anticipate that when the clinical practice will take advantage of the genetic information of the diabetic patients, this will provide a useful resource for the prevention of T2DM progression, enabling the identification of the precise drug that is most likely to be effective and safe for each patient and the reduction of the economic impact on a global scale.

KEYWORDS

pharmacogenetics, precision medicine, T2DM, translational medicine, type 2 diabetes mellitus

1 | INTRODUCTION

Diabetes mellitus is one of the leading causes of mortality worldwide and is a major cause of blindness, kidney failure, heart attacks, stroke, and lower-limb amputation.¹ The number of people with diabetes has risen from 108 million in 1980,¹ to 425 million in 2017, and is still increasing.² Type 2 diabetes (T2DM) accounts for around 90% of all

diabetes cases; it mainly settles because of the body's ineffective use of insulin and inability of pancreatic β cells to compensate for the enhanced insulin demand resulting in uncontrolled glucose homeostasis.^{1,2} Over time, poor glycemic control affects several body districts, especially blood vessels and nerves, fostering the development and progression of neuropathies, micro and macrovascular complications, and premature death.¹

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Interindividual variability in therapeutic response is partly due to genetic heterogeneity, and pharmacogenomics is the discipline that investigates how our entire genome influences individual responses to drugs, and more specifically, pharmacogenetics focuses on genetic variation at a population level, and how these variants can affect therapeutic outcomes and incidence of adverse effects.³ Pharmacogenetics, therefore, is a key component of the translational medicine effort. Nowadays, genetic investigation has reached an incredible depth of information; single nucleotide polymorphism (SNP) arrays and Next Generation Sequencing allow the screening of common and rare genetic variants in our genome, with an unprecedented throughput. These instruments have already been implemented for the diagnostic processes of pathologic phenotypes and to model prediction of complex traits, through the creation of panels enriched with preselected informative targets for diagnostic and research purposes. Oddly enough, pharmacogenetic studies on oral and injectable anti-hyperglycemic drugs have been piling up in the literature, but this ever-increasing amount of knowledge is far from being translated into clinical practice to help define the best therapeutic choice for patients with T2DM. The aim of this comprehensive review is to discuss pharmacogenetic evidences published until March 2018, according to T2DM pharmacotherapy class (metformin [MET], sulfonylureas/glinides [SUF], thiazolidinediones [TZDs], and GLP-1 receptor agonists/DPP-4 inhibitors), in the effort of providing a critical interpretation of existing findings to offer an overview for their future translation. Defining the nature of drug-gene interactions and identifying means through which trustworthy observations can be translated into clinical practice settings might help decision-making about the therapeutic approach through precision medicine strategies, ameliorate cost-effectiveness of existing treatments, and reduce avoidable adverse side effects.

2 | RESEARCH METHODS

A literature search was performed using MEDLINE with the following search terms:

("diabetes mellitus, type 2"[MeSH Terms] OR "diabetes mellitus, type 2"[MeSH Major Topic] OR t2 dm[Title/Abstract] OR NIDDM [Title/Abstract] OR type 2 DM [Title/Abstract] OR type II DM [Title/Abstract] OR diabet*[Title/Abstract] AND (type 2[Title/Abstract] OR type-2[Title/Abstract] OR type II [Title/Abstract] OR non-insulin dependent [Title/Abstract])) AND ("pharmacogenetics"[MeSH Major Topic] OR "pharmacogenetics"[MeSH Terms] OR pharmacogen*[Title/Abstract] OR "precision medicine"[MeSH Major Topic] OR "precision medicine"[MeSH Terms] OR ("precision"[Title/Abstract] OR "tailored"[Title/Abstract] OR "personalized"[Title/Abstract] OR "individualized"[Title/Abstract]) AND ("therapy"[Title/Abstract] OR "medicine"[Title/Abstract] OR "clinical practice"[Title/Abstract]) AND ("genetics"[Title/Abstract] OR "polymorphism"[Title/Abstract] OR "snp"[Title/Abstract] OR "gwas"[Title/Abstract] OR "genome wide association"[Title/Abstract])) AND "english"[Language].

Manual integration with the bibliography from the most extensive reviews on the topic has also been carried out.

Summary box

For each class of oral antidiabetic drugs, we reviewed pharmacogenetic reports supporting

- associations at GWAS level of significance;
- associations replicated in multiple studies;
- associations with nominal significance lacking replication (supplementary material).

We collectively identified 64 genes and approximately 200 informative genetic variants. The most robust evidence to support specific, biologically plausible, gene-drug interactions, regarded

- Several members of the organic cation transporter family (OCTs), *ATM* and *SLC2A2* loci with MET response;
- *CYP2C9*, *TCF7L2*, *ABCC8*, *KCNJ11* and *IRS1* loci with SUF response;
- *PPARG* locus with TZDs response;
- *GLP1R* locus with DPP-4 inhibitors/GLP-1 receptor agonists response.

3 | SUMMARY OF THE LITERATURE

3.1 | Polymorphisms affecting MET response

Metformin (MET) is the only component of the biguanides class used in clinical practice. MET has been the first line approach for T2DM patients of novel diagnosis for decades; it produces durable anti-hyperglycemic effects independently of body weight, carries a low risk of hypoglycemia, and has robust cardiovascular safety profile. For all these reasons, MET is the first choice treatment recommended by guidelines and is suitable for combination therapies with all other hypoglycemic agents. It has been showed that genetic factors influence glycemic response to MET, with a heritability of 34% for the absolute reduction in HbA1c, adjusted for pretreatment values (Table 1).⁴

3.1.1 | Associations at GWAS level of significance

In the first Genome Wide Association study (GWAs) of MET response performed in two independent subsets of the GoDART cohort and in the UKPDS, both composed of European subjects affected by T2DM, the C allele of rs11212617 was found to be associated with reduced glycemic response to MET (odds ratio [OR] for the ability to achieve a treatment HbA1c <7% in the 18 months after starting MET = 1.35 95% CI 1.22-1.49).⁵ rs11212617 is located downstream the gene coding for the *ATM* serine/threonine kinase, associated with *ataxia telangiectasia*. After discovery, the researchers were able to link *ATM* to MET action through functional studies in vitro.⁵ Although the

TABLE 1 Summary of genetic variants that influence metformin therapy outcomes in at least one ethnic group

†Gene	‡SNP	‡Alleles	‡Region	‡Start Position (bp)	Function	Associated Traits	Adverse effect	References
Associations at GWAS level of significance								
ATM	rs11212617	C/A	11q22.3	108412434	Intron	MET response		5, 6
SLC2A2	rs8192675	A/G	3q26.2	171007094	Intron	MET response		10
Associations replicated in multiple studies								
SLC22A2	rs316019	G/T	6q25.3	160249250	Missense Ala270Ser	MET PK, HbA1c	MET tolerance	40, 41, 43-47, 50
	rs145450955	G/A		160250619	Missense Thr201Met			
	rs201919874	C/T	160250625	Missense Thr199Ile	MET PK			
	rs3119309	C/T	160264040	Intron	MET response, MET PK			
	rs7757336	G/T	160268526	Intergenic				
rs2481030	A/G	160335403						
IRS1	rs1801278	G/A	2q36.3	226795828	Missense Gly972Arg	Secondary failure		15-17
SLC22A1	rs34447885	C/T	6q25.3	160121976	Missense Ser14Phe	MET PK	MET tolerance	20, 21, 23-27, 31-35, 37, 38, 40
	rs1867351	A/G		160122091	Synonymous Ser52Ser			
	rs12208357	C/T	160122116	Missense Arg61Cys	MET PK			
	-	C/A	160122224	Missense Gln97Lys				
	rs200684404	C/T	160122285	Missense Pro117Leu				
	rs4709400	C/G	160122578	Intron	FPG, PPG			
	rs34104736	C/T	160132282	Missense Ser189Leu	MET PK			
	rs756787089	C/T	160132332	Missense Arg206Cys				
	rs36103319	G/T	160132375	Missense Gly220Val				
	rs4646277	C/T	160136228	Missense Pro283Leu				
	rs2282143	C/T	160136611	Missense Pro341Leu				
	rs34130495	A/G	160139792	Missense Gly401Ser				
	rs628031	G/A	160139813	Missense Met408Val	MET response, FPG	Hypoglycemia, MET tolerance		
	rs72552763	-/GAT		160139851	inframe_indel Met420del	MET PK	MET tolerance	
	rs36056065	-/		GTAAGTTG	160139876	Intron		
rs622342	C/A		160151834	Intron	MET response			
rs34059508	A/G		160154805	Missense Gly465Arg	MET PK			
rs2297374	C/T		160154953	Intron	HbA1c, FPI			
SLC47A1	rs77630697	G/A	17p11.2	19542448	Missense Gly64Asp	MET PK		26-28, 30, 48, 51-54, 58-60
	rs77474263	C/T		19548051	Missense Leu125Phe			
	rs35646404	C/T	19549655	Missense Thr159Met				
	rs2289669	G/A	19560030	Intron	MET PK, MET response, HbA1c			
	-	C/T	19560195	Missense Ala310Val	MET PK			
	rs149774861	A/C	19560249	Missense Asp328Ala				
	rs35790011	G/A	19560278	Missense Val338Ile				
	rs8065082	C/T	19561878	Intron	HbA1c, MET response			
	rs76645859	G/A	19572813	Missense Val480Met	MET PK			
	rs35395280	G/T	19577330	Missense Cys497Phe				
SLC47A2	rs34399035	C/T	17p11.2	19681658	Missense Gly429Arg	HbA1c	MET PK	26, 55, 57, 59, 61, 62
	rs373244724	T/C		19706671	Missense Tyr273Cys			
	rs562968062	C/A	19707841	Missense Gly211Val				
	rs146901447	G/A	19712704	Missense Pro162Leu	MET PK, MET response			
	-	C/G	19713960	Missense Pro103Arg	MET PK			
	-	C/A	19715149	Missense Lys64Asn				
	rs12943590	G/A	19716685	5' UTR	MET PK, MET response			
	rs34834489	T/A	19716951	upstream_gene	MET PK			
	rs758427	T/C	19717164	Intron				

†HUGO approved gene symbols.

‡dbSNP record from build 147/GRCh38/hg38 (where available); <http://www.ncbi.nlm.nih.gov/snp/>

Abbreviations: FPI, fasting plasma insulin; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; MET, metformin; PD, pharmacodynamics; PK, pharmacokinetics; PPG, postload or 2-h OGTT plasma glucose.

genetic association was confirmed through a meta-analysis of five cohorts from the United Kingdom and The Netherlands,⁶ more recently, no significant differences in MET's effects by rs11212617 genotype on diabetes incidence or change in insulin sensitivity, fasting

glucose levels, HbA1c, or disposition index were observed either in the large randomized control trial Diabetes Prevention Program (DPP) carried out in individuals with impaired glucose tolerance (IGT)⁷ or in smaller studies.⁸ It is possible that the latter population

studies failed to replicate the original findings because of inadequate statistical power or pharmacogenetic MET-response interaction with rs11212617 may diverge at different stages of impaired glucose metabolism. In addition to this, more recently, enhancer assays of MET-activated epigenetic sites showed increased enhancer activity in the *ATM* intron containing SNPs in LD with rs11212617.⁹ Interestingly, the LD block encompasses several genes including *EXPH5* (Exophilin 5, involved in exosome secretion and intracellular vesicle trafficking) and *DDX10* (DEAD-box helicase 10), which resulted upregulated by MET in vitro, while *ATM* expression was unchanged.⁹

In a meta-analysis performed by the Metformin Genetics (MetGen) Consortium comprising 10 557 participants of European ancestry, a genome-wide statistically significant association was found for the intronic SNP rs8192675, located within *SLC2A2*, which encodes the GLUT2 glucose transporter.¹⁰ Each copy of rs8192675 C allele was associated with a greater MET-induced HbA1c reduction of 0.17% ($P = 6.6 \times 10^{-14}$), which was attenuated after adjusting for baseline HbA1c (reduction of 0.07%; $P = 2 \times 10^{-8}$). Consistent with the functional relevance of this variant, the C allele was associated with lower expression of GLUT2 in the liver. However, there was no effect of rs8192675 on the efficacy of MET in delaying progression to diabetes in the DPP study, again raising the possibility that MET \times gene interaction in the prediabetic condition might change when T2DM is established.

3.1.2 | Associations replicated in multiple studies

Insulin signalling is triggered by the binding of insulin to the insulin receptor (IR). This activates the IR intrinsic tyrosine kinase activity and promotes tyrosine phosphorylation of IR substrate (IRS) proteins, which serve as a docking station for downstream signal transducers.^{11,12} The most frequent *IRS1* variant is rs1801278 (Gly972Arg),¹¹⁻¹³ and the Arg972 allele is associated with early onset of T2DM;¹⁴ *IRS1* Gly972Arg polymorphism was found to be associated with failure to oral hypoglycemic treatment, mostly MET and SUF, in three Italian case-control studies.¹⁵⁻¹⁷ The relationship between Gly972Arg and efficacy of MET in lowering HbA1c was explored in a small sample of Caucasian T2DM patients, and it returned no significant associations.¹⁸

The Organic Cation Transporter 1 (OCT1), encoded by *SLC22A1* is the main transporter of MET, and highly polymorphic in humans,¹⁹ and several non-synonymous variants modulate MET entrance into target cells. Polymorphism rs628031 (Met408Val) is the only variant identified in all ethnic groups, Europeans, South Americans, Africans, and Asians.¹⁹ Although no associations were found with treatment efficacy in a small European cohort of T2DM patients, carriers of the minor allele (Met408) had a slightly reduced incidence of hypoglycemic events during a 6 months period of combined MET-SUF treatments.²⁰ The variant Met408 and its closely related proxy rs36056065 (8 BP insertion) were shown to predispose to the occurrence of symptoms of MET intolerance in another small cohort of T2DM patients from Latvia.²¹ Earlier studies had proposed Met408Val as predictor for MET treatment efficacy, but genotype/phenotype association has not been consistent across studies.^{8,22-24} In a small case-control study performed on Chinese subjects, the 408Val allele

(the “nonrisk” allele) resulted homozygous in nine out of the 10 patients whose HbA1c declined by less than 1% after 3 months of MET treatment.²⁵ Polymorphism rs622342²⁶ is the only intronic variant identified in all ethnic groups, with the exception of Pacific Islanders,¹⁹ and has been proposed as negative predictor for MET treatment outcomes.^{23,24} In a European cohort study,²⁷ the C allele was associated with greater HbA1c reduction in diabetic subjects treated with MET, but this interaction could not be replicated in other cohorts of similar ethnicity (American-European population^{28,29} and Central European drug naïve T2DM patients).³⁰ Indeed, in a study carried out in 122 newly diagnosed, treatment naïve T2DM patients from South India, carriers of the rs622342 C variant were found to be less responsive to MET action on HbA1c.³¹ In a small clinical trial on patients with castration-resistant prostate cancer, homozygous carriers of the rs622342 C variant showed lower-MET-related toxicity and reduced drug efficacy on prostate cancer progression compared with A allele carriers.³² Caucasian, African, and South American populations share the presence of two variants: rs12208357 (Arg61Cys)²⁶ and a deletion of the methionine codon in position 420, which can be induced by any of three polymorphisms: rs35191146-/G, rs35167514-/ATG, and rs72552763-/TAG.^{19,26} Earlier studies in non-diabetic Caucasian subjects have shown altered MET pharmacokinetics and lower transport in the presence of the SNPs rs12208357 (Arg61Cys), rs34130495 (Gly401Ser), rs72552763 (Met420del), and rs34059508 (Gly465Arg)^{26,33-35}; while, more recently, there was no effect on the pharmacokinetics of MET in patients carrying the supposed reduced-function OCT1 allele at Arg61Cys, Gly401Ser, Met420del or Gly465Arg.³⁶ The same polymorphisms, together with the *SLC22A1* promoter-linked synonymous variant rs1867351 (Ser52Ser), were associated with an increase in the renal clearance of MET, possibly driven by a reduction in OCT1 expression or activity.³⁷ Similarly, in a small cohort of European T2DM patients, the number of OCT1 reduced-function alleles in Arg61Cys and Met420del was significantly associated with two-fold higher odds of the common MET-induced gastrointestinal side effects³⁸; nevertheless, a large randomized control trial performed on Scottish subjects (GoDART) and a large-scale meta-analysis on subjects of European ancestry (MetGen) showed no clinically evident reduction in the ability of MET to lower HbA1c in individuals with T2DM in presence of the variants Arg61Cys and Met420del.^{29,39} A small case-control study performed on Chinese T2DM subjects, depicted peculiar phenotype patterns for Ser52Ser and two intronic polymorphisms, rs4709400 and rs2297374.²⁵ Ser52Ser-affected HbA1c and postprandial plasma glucose response to MET, rs4709400 affected both fasting and postprandial glucose MET modulation, and rs2297374 modulated HbA1c and fasting insulin levels.²⁵ Experimental studies have demonstrated that OCT1-mediated MET uptake is reduced in oocytes expressing rs2282143 (Pro341Leu) and rs4646277 (Pro283Leu).⁴⁰ Pro341Leu is highly frequent in the Asiatic population; a trend toward higher MET bioavailability was reported in Korean subjects, although it was not statistically significant, and the analyses were not corrected for possible confounders.⁴¹ Of much rarer distribution, the following variants have only been assayed in vitro: rs34104736 (Ser189Leu) and rs36103319 (Gly220Val) have been involved with reduced MET transport, rs34447885 (Ser14Phe) was shown to increase MET

uptake,³³ and cells expressing the extremely rare mutation Gln97Lys, rs200684404 (Pro117Leu), or rs756787089 (Arg206Cys) had reduced MET uptake and pharmacokinetics.²⁴

SLC22A2 encodes the Organic Cation Transporter 2 (OCT2), which has strong affinity for MET.⁴² The intergenic variants rs3119309, rs7757336, and rs2481030 located between SLC22A2 and SLC22A3 within a linkage block, have been recently associated with the lack of response to MET in a small group of Caucasian patients with T2DM and reduced levels of circulating MET in carriers of the risk alleles.⁴³ Three nonsynonymous variants, rs145450955 (Thr201Met), rs316019 (Ala270Ser), and rs201919874 (Thr199Ile), were repeatedly shown to influence MET uptake, tubular excretion and clearance, consistent with an increase in circulating MET concentrations, both in vitro and in vivo.^{40,41,44-47} Among Iranian T2DM patients treated with MET, carriers of 201Met exhibited higher-HbA1c concentrations, fasting glucose levels, and homeostasis model assessment of insulin resistance (HOMA-IR), and a possible sex specificity, which had never been reported previously.⁴⁸ In a small number of Chinese T2DM patients of novel diagnosis, a significantly stronger decrease in HbA1c was observed in heterozygous compared with wild-type 270Ala homozygous after 1 year of treatment with MET, upon adjustment for baseline HbA1c, exercise, and diet.⁴⁷ No effects of Ala270Ser on MET pharmacokinetics or pharmacodynamics were detected in a small group of nondiabetic Korean subjects.⁴⁹ Ala270Ser exhibited no genotype/phenotype association when studied in Caucasian subjects.^{28-30,37}

Notably, in 2013, it has been suggested that interaction with variants in the multidrug and toxin extrusion (MATE) 1 transporter (SLC47A1) may mask SLC22A2 Ala270Ser effects on MET clearance.⁵⁰ Several studies performed in European subjects have identified an association between the intronic variants of SLC47A1 rs2289669 and rs8065082 (closely in linkage disequilibrium) and response to MET in subjects with T2DM.^{26,28,51} Individuals who were homozygous for SLC22A1 rs622342C allele exhibited a larger-MET glucose-lowering effect, which was exacerbated in presence of one or two SLC47A1 rs2289669A alleles.^{27,51,52} rs2289669A by itself was associated with greater HbA1c decline in newly diagnosed T2DM patients of Chinese,⁵³ Iranian,⁵⁴ and European³⁰ ethnicity. Newly diagnosed Chinese T2DM patients and healthy Koreans carrying the rs2289669A allele exhibited lower-MET excretion and renal clearance.^{49,53} However, rs2289669 showed no association with MET clearance in studies performed in Caucasian nondiabetic³⁷ and T2DM patients,^{29,55} independently of SLC22A1 rs622342 genotype.^{29,55} Using knockout experiments on mice, it has been revealed that alterations of SLC47A1 sequence on both chromosomes are required in order for MET to accumulate in the liver, fostering lactic acidosis.^{56,57} It is, then, likely that inconsistencies about the effects of rs2289669 and rs622342 might depend on other, more dramatic, mutations of SLC47A1, occurring at an independent site, such as the five nonsynonymous variants, identified in a multiethnic nondiabetic cohort, associated with reduced MET transport in vitro⁵⁸⁻⁶⁰: rs77630697 (Gly64Asp), rs77474263 (Leu125Phe), rs35790011 (Val338Ile), rs76645859 (Val480Met), and rs35395280 (Cys497Phe).⁵⁸ Additionally, three nonsynonymous variants were demonstrated to be associated with reduced MET transport in vitro:

rs149774861 (Asp328Ala), the extremely rare mutation Ala310Val, and rs35646404 (Thr159Met) exclusive of Asiatic populations.^{59,60}

SLC47A2 encodes for the transporter MATE2, highly homologous to MATE1, and, as the latter, is involved in excretion of endogenous and exogenous toxic electrolytes through urine and bile. Several non-synonymous variants in SLC47A2 sequence exhibited reduced MET transport activity in vitro: The transcript in presence of the rare mutations Lys64Asn,⁵⁹ rs562968062 (Gly211Val),^{57,59} and rs146901447 (Pro162Leu)⁵⁷ were not detectable in engineered HEK293 cells, while Tyr273Cys was localized to the wrong cellular compartments.⁵⁷ By contrast, the variant Pro162Leu seemed to increase the response to MET in vivo in a cohort of African American subjects.⁶¹ The rare mutation Pro103Arg was found to be correctly expressed at the plasma membrane and to overdouble MET transport activity.⁵⁷ Finally, rs34399035 (Gly429Arg) was the only nonsynonymous variant apparently affecting the long-term decrease in HbA1c in European Caucasians, with carriers of the variant showing a 0.8% (95% CI, 0.02-1.6; $P = 0.05$) lower decrease than the wild-type carriers.⁵⁵ The intronic polymorphism rs12943590 was associated with reduced clinical response to MET in US diabetic subjects of African or European ancestry.^{26,61} The non-coding variant rs12943590, in the 5' UTR, was found to induce no pharmacokinetic differences in Koreans⁴¹ and in a large meta-analysis performed on European T2DM subjects;²⁹ nevertheless, a small group of Korean nondiabetic volunteers carrying rs12943590 or rs758427 and rs34834489 exhibited increased promoter activity, with a significant raise in renal and secretion clearance.⁶²

3.1.3 | Associations with nominal significance lacking replication (supporting information)

3.2 | Polymorphisms affecting SUF/meglitinides response

For years, the drug of choice alongside MET has belonged to the family of SUF/glinides. Both pharmaceutical classes carry weight gain as side effect and a high risk of hypoglycemia.⁶³ SUF bind the ATP-dependent K⁺ (KATP) channels on beta-cells membrane therefore inducing K⁺ entrance into the cell, the depolarization of the plasma membrane, and the opening of voltage-gated Ca²⁺ channels. The spike of intracellular Ca²⁺ levels triggers insulin zymogen fusion with the plasma membrane and insulin secretion. Over time, the compensatory efforts of the beta cells may eventually lead to a decline of beta-cell mass and secondary failure of sulfonylurea/glinides treatment (Table 2).⁶⁴

3.2.1 | Associations replicated in multiple studies

The gene CYP2C8 encodes for an enzyme belonging to the cytochrome P450 (CYP) superfamily. In presence of the most diffused diplotype, CYP2C8*3, defined by the variants rs11572080 (Arg139Lys) and rs10509681 (Lys399Arg), repaglinide metabolism was reported to be increased,^{65,66} resulting in reduced drug bioavailability.⁶⁷ By contrast, the frequency of CYP2C8*3 carriers was

TABLE 2 Summary of genetic variants that influence sulfonylureas/meglitinides therapy outcomes in at least one ethnic group

†Gene	‡SNP	‡Alleles	‡Region	‡Start Position (bp)	Function	Associated Traits	Adverse Effect	References
Associations replicated in multiple studies								
CYP2C8	rs10509681 (*3)	T/C	10q23.33	95038992	Missense Lys399Arg	SUF PK		65-67
	rs11572080 (*3)	G/A		95067273	Missense Arg139Lys			
CYP2C9	rs1799853 (*2)	C/T	10q23.33	94942290	Missense Arg144Cys	SUF PK	Hypoglycemia	68-82, 87
	rs1057910 (*3)	A/C		94981296	Missense Ile359Leu			
SLCO1B1	rs4149015	G/A	12p12.1	21130388	Upstream gene	Repaglinide response SUF PK		65, 72, 82-95
	rs4149056	T/C		21178615	Missense Val174Ala			
ABCC8	rs757110	T/G	11p15.1	17396930	Missense Ala1369Ser	SUF response		82, 96-98, 100-103, 108, 109
	rs1799859	G/A		17397732	Synonymous Arg1273Arg	SUF response, TG		
	rs1801261	C/T	17415318	Synonymous Thr759Thr	SUF response			
	rs1799854	C/T	17427157	Intron	SUF response, TG			
KCNJ11	rs5210	G/A	11p15.1	17386704	3' UTR	SUF response	Secondary failure	26, 97, 103, 116-121
	rs5219	C/T		17388025	Missense Lys23Glu			
KCNQ1	rs2237892	C/T	11p15.4	2818521	Intron	Repaglinide response SUF response, FPG Repaglinide response		127-129
	rs163184	T/G		2825839				
	rs2237895	A/C		2835964				
NOS1AP	rs10494366	G/T	1q23.3	162115895	Intron	SUF response Repaglinide response, FPG, FPI, HbA1c	Mortality	131, 132, 134
	rs12742393	A/C		162254796				
IRS1	rs1801278	G/A	2q36.3	226795828	Missense Gly972Arg	SUF response, insulin secretion	Secondary failure	15, 18, 20, 135, 136
TCF7L2	rs7903146	C/T	10q25.2	112998590	Intron	SUF response	Secondary failure	142-144
	rs12255372	G/T		113049143				
	rs290487	C/T	10q25.3	113149972		Repaglinide response		

†HUGO approved gene symbols.

‡dbSNP record from build 147/GRCh38/hg38 (where available); <http://www.ncbi.nlm.nih.gov/snp/>

Abbreviations: FPG, fasting plasma glucose; FPI, fasting plasma insulin, HbA1c, glycated haemoglobin; PK, pharmacokinetics; SUF, sulfonylureas/meglitinides; TG, triglycerides.

reported to be higher in a small group of T2DM patients who experienced hypoglycemic events while undergoing treatment with SUF (glimepiride, gliclazide, or glipizide) in respect to wild-type CYP2C8*1 homozygous subjects, but this difference was not statistically significant.⁶⁸ The closely related CYP2C9 enzyme is the major responsible for SUF breakdown. The non-synonymous variants rs1799853 (Arg144Cys) and rs1057910 (Ile359Leu), respectively defined as CYP2C9*2 and CYP2C9*3, have been reported to determine lower-CYP2C9 catalytic activity,⁶⁹⁻⁷² resulting in reduced SUF clearance and higher-drug bioavailability across different ethnicities.^{70,73-79} Of notice, these evidences translate into increased odds of moderate to severe hypoglycemic events during treatment with SUF.^{68,80-82} However, CYP2C9*2 and *3 have been shown not to carry increased risk of hypoglycemia in healthy volunteers and T2DM patients taking glimepiride, glibenclamide, gliquidone,^{69,78,83,84} or nateglinide.^{72,85} Caution should be advised when interpreting these data because it has been recently demonstrated that CYP2C9 catalytic impairment might be counteracted by the effects of genetic variation at the CYP oxidoreductase (POR) gene, which is tightly associated with CYP enzymes and can modulate their activity;⁸⁶ indeed, in a subset of subjects from the GoDART database, it has been reported that the number of CYP2C9*2 and *3 alleles was associated with nearly three-fold increased risk of hypoglycaemic events and better response to SUF only in patients carrying the POR*1/*1 wild-type genotype.⁸⁷

The solute carrier organic anion transporter 1B1 (SLCO1B1) encodes for a transmembrane receptor protein, called OATP1B1,

involved in the removal of anionic compounds from the blood into the hepatocyte. SLCO1B1 locus is highly polymorphic; its best characterized non-synonymous variant, rs4149056 (Val174Ala), has been demonstrated to significantly increase repaglinide bioavailability in both T2DM and healthy subjects of Caucasian and Asian ethnicity.^{65,88-93} A larger concentration of nateglinide in the presence of the low-metabolizing variant 174Ala has also been reported,^{72,94} but the association has not been consistent throughout other studies.^{89,91}

The non-coding SNP rs4149015, located less than 1 kb upstream SLCO1B1 has been found to be associated with an increased glucose-lowering effect of repaglinide,⁶⁵ an effect that could be attributed to the close proximity with rs4149056 polymorphism.⁹⁵

The ABCC8 gene encodes for a member of the superfamily C of ATP-binding cassette (ABC) transporters, which functions as a modulator of KIR6.2 transporters (encoded by KCNJ11), and together, they form KATP channel complexes. Several SNPs within the ABCC8 locus have been associated to interindividual variability in the response to SUF treatment. The intronic polymorphism rs1799854 (exon 16 -3C → -3 T), often combined with the closely linked non-synonymous variant rs1801261 (Thr759Thr),²⁶ has been associated with reduced insulin secretion after tolbutamide infusion in nondiabetic relatives of T2DM patients.⁹⁶ T2DM patients on SUF treatment carrying the rs1799854C/C genotype exhibited significantly lower-HbA1c levels compared with the patients with T/T genotype and improved insulin sensitivity determined by HOMA index in response to repaglinide, with respect to T carriers.^{97,98} However, rs1799854 was not

associated with early failure of SUF therapy in a cross-sectional study performed on a small cohort of T2DM patients.⁹⁹ T2DM patients on SUF treatment carrying the G/G genotype of the synonymous SNP rs1799859 (Arg1273Arg) had significantly higher-HbA1c levels compared with the patients with A/A genotype,⁹⁸ thus implying lower-SUF efficacy. In the same study, no effect of rs757110 (Ala1369Ser) was observed on SUF ability to modulate either fasting and postprandial glucose levels or HbA1c.⁹⁸ The latter result has been confirmed in several studies across different ethnicities.^{82,100,101} ten combined with the Nevertheless, in two studies, both performed on Chinese T2DM patients, homozygous carriers of the 1369Ala allele were reported to exhibit enhanced glicazide efficacy.^{102,103} The ability of *ABCC8* polymorphism Ala1369Ser to interfere with SUF therapy is peculiarly controversial because this SNP is in strong linkage disequilibrium with the non-synonymous variant Lys23Glu in *KCNJ11*,^{104,105} and it is possible to postulate the existence of a molecular selective specificity for the genetic variation at KATP channels.¹⁰⁶ Indeed, when compared with *ABCC8-KCNJ11* wild-type haplotype carriers, 1369Ala-23Lys haplotype was shown to increase sensitivity to gliclazide, and mitiglinide,^{106,107} whereas it was less responsive to tolbutamide, chlorpropamide, and glimepiride,¹⁰⁶ and no differences have been observed with the use of nateglinide, repaglinide, glipizide, and glibenclamide.^{84,106,107} Finally, both *ABCC8* polymorphisms rs1799854 and rs1799859 resulted associated with circulating triglycerides level after SUF therapy.^{108,109}

KCNJ11 (potassium voltage-gated channel subfamily J member 11) encodes for the pore forming subunit (also named KIR6.2) of the KATP channel designated to modulate glucose-dependent insulin secretion in pancreatic beta cells. Large studies have been able to prove that the non-synonymous polymorphism rs5219 (Lys23Glu)²⁶ is more frequent in T2DM^{102,105,110-112} and in subjects with decreased insulin secretion,¹¹³ although initial reports documented no association between genetic variants in *KCNJ11* and T2DM.^{104,109,114,115} In vitro experiments in human pancreatic islets have demonstrated a reduction in response to SUF in presence of the non-synonymous polymorphism 23Lys,¹¹⁶ which has been confirmed in studies performed on T2DM patients of Chinese ethnicities undergoing SUF therapy,¹¹⁷ alongside the nearby non-coding variant rs5210.^{26,103} Consistent with the previous observations, 23Lys carriers have been reported to exhibit higher predisposition to secondary failure when treated with SUF.^{116,118-120} By contrast, studies performed on T2DM patients of Caucasian¹²¹ and Asian⁹⁷ descent have observed a positive effect of the variant 23Lys in response to SUF or no significant differences in the glucose lowering action of the drug.^{98,111} The risk of hypoglycemic events commonly associated with SUF therapy has been found to be independent from the presence of the Lys23Glu variant¹²² or its non-synonymous proxy rs5215 (Val337Ile).⁸²

The *KCNQ1* gene, located on chromosome 11, belongs to a large family of voltage-gated K⁺ channels. The intronic variant rs2237895 in *KCNQ1* has been found to be associated with reduced insulin secretion in cross-sectional and prospective studies, conferring increased T2DM risk across different ethnicities.¹²³⁻¹²⁶ The intronic polymorphisms rs2237892 and rs2237895 were shown to increase repaglinide sensitivity,^{127,128} whereas a third intronic variant, rs163184, was reported to lower-SUF effects on fasting plasma glucose levels.¹²⁹

The gene *NOS1AP* encodes for the nitric oxide synthase (NOS) 1 adaptor protein, which downregulates the neuronal NOS1 and Ca²⁺ influx channels. The SNP rs10494366 in the *NOS1AP* gene has been associated with QTc prolongation.¹³⁰ In the Rotterdam study, a population-based cohort study of elderly people, carriers of the TG or GG genotype at rs10494366 treated with glibenclamide exhibited higher-glucose levels and mortality rates compared with glibenclamide users with the TT genotype.¹³¹ In addition, in Chinese patients with T2DM, the TT genotype was associated with an increased effect of repaglinide on insulin resistance measured by HOMA index.¹³² By contrast, pharmacodynamics studies carried out in Korean healthy volunteers showed no statistically significant differences based on rs10494366 genotype.⁸⁴ The intronic variant rs12742393 has been associated with T2DM in a cohort of Chinese patients with the C allele showing significant risk for diabetes with an OR of 1.17 (95% CI, 1.07-1.26, *P* = 0.0005).¹³³ Indeed, the effects of repaglinide treatment on fasting plasma glucose, insulin levels, and HOMA-IR index were reduced in patients with T2DM carrying the *NOS1AP* rs12742393 risk C allele compared with carriers of the AA genotype.¹³⁴

As anticipated in Section 3.1.2, *IRS1* plays a pivotal role in the transduction of the insulin signalling cascade. The most frequent variant of *IRS1*, Gly972Arg, was found to be associated with failure of the hypoglycemic treatment with SUF in five case-control studies.^{15-18,120} Furthermore, diabetic patients carrying the Arg972 variant receiving treatment with insulinotropic hypoglycaemic drugs such as SUF and/or gliinides had higher-HbA1c levels compared with wild-type carriers.¹⁸ In vitro experiments performed on a rat beta-cell line and isolated human islets have proven that the risk allele 972Arg is associated with a marked reduction of insulin secretion in response to SUF.^{135,136}

The locus of transcription factor 7-like 2 gene (*TCF7L2*) is the strongest known signal associated with T2DM.¹³⁷ Consistent evidences have been reported for the intronic polymorphisms of *TCF7L2* (rs12255372 and rs7903146) with increased risk of T2DM.¹³⁸⁻¹⁴¹ Both risk alleles have also been associated to reduced response to SUF treatment in a large randomized control trial on European subjects,¹⁴² and rs7903146 polymorphism was associated to SUF treatment failure in an independent study on T2DM German patients.¹⁴³ A pharmacogenetic study in Asian subjects has assessed the effects exerted on glimepiride hypoglycemic efficacy by several intronic variants in the *TCF7L2* locus, in a small number of healthy volunteers⁸⁴; the SNPs rs290487, rs11196205, and rs12255372, along with rs7903146, showed no differences when compared with the wild-type alleles,⁸⁴ although the variant rs290487 had previously been identified as a modulator of repaglinide therapeutic action in Chinese T2DM patients.¹⁴⁴

3.2.2 | Associations with nominal significance lacking replication (supporting information)

3.3 | Polymorphisms affecting TZDs response

Since the late 1990s, TZDs are a therapeutic option for patients with T2DM in whom they act by improving insulin sensitivity and preserving β -cell secretory function. The net effect of TZDs is an increased

mass of small insulin-sensitive subcutaneous adipocytes with decreased lipolytic activity, resulting in decreased free fatty acids concentration and improved adipocytokine profile.¹⁴⁵ Similarly to SUF and insulin treatment, TZDs may lead to weight gain, partly because of TZDs' most common side effect, fluid retention, which might foster the formation of peripheral edema in patients with cardiac or renal disease.¹⁴⁶ Because of the potential for long-term adverse effect, TZDs use has been subject of debate with one molecule in this class, troglitazone (TRO) being taken off-market since the year 2000, because of increased incidence of drug-induced hepatitis and rosiglitazone (ROSI) being suspected of bringing cardiovascular harm and retracted by the Food and Drug Administration at first, but later, it has been restored in the US market.¹⁴⁷ Pioglitazone (PIO) is the only TZD still marketable in Europe, and it has actually been reported to improve cardiovascular events in patients with T2DM and in insulin resistant nondiabetic individuals (Table 3).¹⁴⁸⁻¹⁵⁰

3.3.1 | Associations replicated in multiple studies

Multiple cytochrome P450 enzymes are involved in the metabolism of TZDs; however, CYP2C8 (previously discussed in Section 3.2.1) is responsible for the catalysis of most of the biotransformation of PIO and ROSI.^{66,151-155} Its most frequent haplotype is CYP2C8*3, mainly found in Caucasians and Hispanics, designated by the presence of two non-synonymous polymorphisms: rs11572080 Arg139Lys and rs10509681 Lys399Arg.^{155,156} Carriers of CYP2C8*3 were shown to have significantly lower-ROSI area under the curve (AUC), higher-oral clearance,¹⁵⁷ lower OR of developing edema,¹⁵⁸ and a statistically significant reduced response to ROSI treatment,^{158,159} although one early study in a very small cohort detected no association of CYP2C8*3 with the drug glucose-lowering effect.¹⁶⁰ CYP2C8*3 polymorphisms were shown to reduce PIO AUC as well, resulting in higher-PIO clearance.¹⁶¹⁻¹⁶⁴ CYP2C8*11, identified by the presence of the infrequent nonsense variant rs78637571 Glu274Stop in subjects of East Asian ethnicity, was reported to increase ROSI AUC

and bioavailability in heterozygous subjects.¹⁶⁵ Finally, the polymorphism rs11572103 Ile269Phe, designated as CYP2C8*2, has been reported to influence PIO pharmacokinetics in vivo in African Americans.¹⁶⁶

PPARG is a nuclear receptor serving as lipid sensor and the cognate receptor for TZDs¹⁶⁷; its most common variant, rs1801282 (Pro12Ala), reproducibly associated with decreased risk of T2DM,¹⁶⁸⁻¹⁷¹ has been widely addressed in pharmacogenetics studies on TZDs efficacy. Several reports have been meta-analysed revealing a better response to PIO treatment in terms of improvements in fasting glucose, HbA1c and triglycerides in carriers of the 12Ala allele^{164,172-174} despite two studies observed no association,^{175,176} and one reported that insulin levels and insulin resistance were lower in carriers of the Pro12Pro genotype after PIO treatment.¹⁷² In response to ROSI, Korean T2DM patients carrying the 12Ala variant have been shown to have significantly greater decrease in fasting glucose levels and HbA1c.¹⁷⁷ Earlier studies evaluating how the common genetic variation in PPARG influenced TRO efficacy have revealed a nominal association for multiple SNPs,¹⁷⁸ but several smaller and larger study groups failed at replicating the previously reported associations.^{175,179,180}

The docking of PPARG to the transcription factor coactivator PPARGC1A allows the recruitment of two transcription factors to form a highly efficient transcription complex. In Chinese T2DM patients, the non-synonymous polymorphisms (Thr394Thr; rs2970847 and Gly482Ser; rs8192678) in PPARGC1A appear to influence patient response to ROSI therapy.^{158,173,181} To date, no significant differences were observed when the effects of Gly482Ser were evaluated in patients treated with PIO.¹⁷³

ADIPOQ encodes the anti-inflammatory cytokine adiponectin, solely expressed in adipose tissue. The variant rs266729, located approximately 1 kb upstream ADIPOQ has been shown to induce greater changes in fasting glucose and HbA1c after treatment with PIO in a study conducted in Chinese T2DM patients,¹⁸² and carriers of the homozygous wild-type rs266729 genotype, undergoing treatment with ROSI, exhibited a greater reduction in fasting plasma

TABLE 3 Summary of genetic variants that influence thiazolidinediones therapy outcomes in at least one ethnic group

†Gene	‡SNP	‡Alleles	‡Region	‡Start Position (bp)	Function	Associated Traits	Adverse Effect	References
Associations replicated in multiple studies								
CYP2C8	rs10509681 (*3)	C/T	10q23.33	95038992	Missense Lys399Arg	TZD PK	Edema	157-159, 161-166
	rs78637571 (*11)	C/A		95045951	Stop gained Glu274Stop	ROSI PK		
	rs11572103 (*2)	A/T		95058349	Missense Ile269Phe	PIO PK		
	rs11572080 (*3)	A/G		95067273	Missense Arg139Lys	TZD PK, ROSI response	Edema	
PPARG	rs1801282	C/G	3p25.2	12351626	Missense Pro12Ala	TZD response, FPG, HbA1c, TG		164, 172-174, 177
PPARGC1A	rs8192678	A/G	4p15.2	23814039	Missense Gly482Ser	ROSI response		158, 173, 181
	rs2970847	C/T		23814301	Synonymous Thr394Thr			
ADIPOQ	rs266729	C/G	3q27.3	186841685	Upstream gene	TZD response, FPG, HbA1c		182-184, 186
	rs2241766	A/C		186853103	Synonymous Gly15Gly			
	rs1501299	G/T		186853334	Intron	ROSI response, FPG, HbA1c		

†HUGO approved gene symbols.

‡dbSNP record from build 147/GRCh38/hg38 (where available); <http://www.ncbi.nlm.nih.gov/snp/>

Abbreviations: FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; PIO, pioglitazone; PK, pharmacokinetics; ROSI, rosiglitazone; TG, triglycerides; TZDs, thiazolidinediones.

glucose levels.^{182,183} Another study conducted in diabetic subjects from Southern China has shown that the synonymous T45G polymorphism at rs2241766 (Gly15Gly) is related to PIO response in T2DM with patients carrying the TG genotype exhibiting a greater reduction in HbA1c,¹⁸⁴ whereas no evidence of pharmacogenetic influence on HbA1c or fasting glucose levels was observed in response to PIO treatment in Iranian T2DM patients.¹⁸⁵ Together with rs2241766 polymorphism, the intronic SNP rs1501299 has been shown to be associated with reduced fasting glucose and HbA1c levels after ROSI therapy,¹⁸⁶ while opposing evidences were reported in a large cohort of Chinese patients in which the therapeutic efficacy of multiple-dose ROSI was assessed.¹⁸³

3.3.2 | Associations with nominal significance lacking replication (supporting information)

3.4 | Polymorphisms affecting DPP-4 inhibitors/GLP-1 receptor agonists response

Dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon like peptide 1 (GLP-1) receptor (GLP-1R) agonists are considered effective options to lower glucose levels because they carry moderate to low risk of

hypoglycemia, thus offering better life-quality expectancies to the patients. Because the incretin hormones GLP-1 and GIP (gastric inhibitory polypeptide) are rapidly cleaved into the bloodstream by DPP-4 into inactive forms, DPP-4 inhibitors have been developed to increase circulating incretins level, for the treatment of T2DM.¹⁸⁷ GLP-1R agonists, by definition, explicate their function by triggering the GLP-1R cascade.¹⁸⁸⁻¹⁹⁰ Adverse effects induced by GLP-1R agonists include transient nausea, vomiting, and diarrhoea,¹⁹¹ although prescription to patients with a history of pancreatitis, medullary thyroid carcinoma, and multiple endocrine neoplasia syndrome type 2 should be made with caution (Table 4).¹⁹²

3.4.1 | Associations at GWAS level of significance

Although several naturally occurring non-synonymous polymorphisms in the gene coding for gastric inhibitory polypeptide receptor (GIPR) have been characterized, the polymorphism rs13306399 (Cys46Ser) was the only one capable of altering the binding of GIP,¹⁹³ while both rs13306399 and rs13306403 (Arg316Leu) have been shown to decrease GIP sensitivity in beta cells in vitro.¹⁹³ The same polymorphisms, together with the infrequent variants rs13306398 (Gly198Cys) and rs1800437 (Glu354Gln), are also associated with reduced cell surface expression and basal receptor signalling.¹⁹³

TABLE 4 Summary of genetic variants that influence DPP-4 inhibitors/GLP1R agonists therapy outcomes in at least one ethnic group

†Gene	‡SNP	‡Alleles	‡Region	‡Start Position (bp)	Function	Associated Traits	Adverse effect	References
Associations at GWAS level of significance								
GIPR	rs13306399	C/G	19q13.32	45670699	Missense Cys46Ser	GIP sensitivity, GIP expression		193-196, 198, 199
	rs13306398	G/T		45674785	Missense Gly198Cys	GIPR expression		
	rs13306403	G/T		45677928	Missense Arg316Leu	GIP sensitivity, GIP expression		
	rs1800437	C/G		45678134	Missense Glu354Gln	GIPR expression	CVD	
	rs10423928	A/T		45679046	Intron	GIP response, PPG, PPI, BMI, Osteopontin, GIPR expression		
QPCTL	rs2287019	C/T		45698914	Intron	FPG, PPG		198, 201
GLP1R	rs10305420	C/T	6p21.2	39048860	Missense Pro7Leu	Liraglutide response		197, 203-210, 214-216
	rs3765467	C/T		39065819	Missense Arg131Gln	GLP1 response		
	rs367543060	C/T		39066240	Missense Thr149Met			
	rs6923761	A/G		39066296	Missense Gly168Ser	Liraglutide response, DPP4i response, PPG, BMI		
	rs10305492	A/G			39079018	Missense Ala316Thr	FPG, PPG, PPI	
rs10305493	C/G		39079155	Missense Ser333Cys	GLP1R binding			
Associations replicated in multiple studies								
KCNQ1	rs151290	A/C	11p15.4	2800385	Intron	Incretin response, GLP-1 levels, PPI		123-126, 219-221
	rs2237892	C/T		2818521				
	rs163184	C/A		2825839				
	rs2237895	A/C		2835964				
	rs2237897	C/T		2837316				
TCF7L2	rs7903146	C/T	10q25.2	112998590	Intron	GLP1 response, DPP-4i response, Hb1Ac		221,225-227
	rs12255372	G/T		113049143			GLP1 response	

†HUGO approved gene symbols.

‡dbSNP record from build 147/GRCh38/hg38 (where available); <http://www.ncbi.nlm.nih.gov/snp/>

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DPP-4i, DPP-4 inhibitors; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; PPG, postload or 2-h OGTT plasma glucose; PPI, postload 2-h OGTT plasma insulin.

Polymorphism rs1800437 was further involved with cardiovascular disease incidence¹⁹⁴ and cultured adipocytes carrying the rs1800437 minor C allele manifested a drastic downregulation of the receptor desensitization-resensitization cycle.¹⁹⁵ The A allele of the intronic variant rs10423928 was associated with a lower amount of the splicing isoform required for transmembrane activity.¹⁹⁶ Recently a 6 months follow-up study carried out in a small group of T2DM patients found no evidence of association with DPP-4 inhibitors efficacy,¹⁹⁷ although carriers of the A allele had been reported to exhibit 0.09 (CI, 0.07-0.11) mmol/L increase of 2-h postload glucose levels during an OGTT, decreased insulin secretion, and a diminished incretin effect in vivo in large cohort studies,^{198,199} aside of a reduction in body mass index (BMI), lean body mass, and waist circumference.¹⁹⁹ A molecular connection with osteopontin (OPN) was suggested because carriers of rs10423928 had lower-OPN expression in pancreas and adipose tissue, both GIP and OPN modulate cytokine-induced apoptosis.^{196,199} The intron variant rs2287019, falling within the glutaminy-peptide cyclotransferase-like (*QPCTL*) gene, approximately 15 kb downstream *GIPR*, has been associated with BMI at genome-wide level.²⁰⁰ The risk C allele was also reported to be associated with higher fasting glucose but lower 2-h postload glucose concentrations during an OGTT.^{198,201} Taken together, these findings suggest that *GIPR* variants could potentially modulate the response to DPP-4 inhibitors, nevertheless, to date, this effect has not been revealed by clinical studies.^{194,197,202}

The GLP-1 receptor is an important drug target for the treatment of T2DM, and several non-synonymous variants of *GLP1R* have been carefully characterized: rs367543060 Thr149Met variant, identified in one Japanese diabetic subject,²⁰³ induces a significant loss of function in vitro²⁰⁴⁻²⁰⁶ and impairs the insulin secretory response to GLP-1 in vivo.^{203,206} The polymorphism rs10305493 (Ser333Cys) instead has been proven to preserve peptide response.^{205,206} The SNP rs6923761 (Gly168Ser) was nominally associated with reduced insulin secretion in response to GLP-1 infusion during a hyperglycemic clamp in nondiabetic American subjects²⁰⁷ and with a weaker response to the glucose-lowering effect of DPP-4 inhibitors in patients with T2DM.¹⁹⁷ On the contrary, the same polymorphism was associated with higher efficacy of liraglutide,²⁰⁸ and it was shown to increase weight and fat mass loss after liraglutide treatment,^{209,210} different types of diet,²¹¹ or bilio-pancreatic diversion surgery.²¹² In addition, carriers of the rs6923761 A allele had higher basal GLP-1 levels²¹⁰ and a better cardio-metabolic profile.²¹³ When the diplotype rs6923761 (Gly168Ser)/rs10305420 (Pro7Leu) was studied, the wild-type form 7Pro, combined with the mutated 168Ser appeared to give an even bigger contribution to the efficacy of treatment with liraglutide.²⁰⁸ Heterozygous carriers of the minor allele of rs3765467 (Arg131Gln) were reported to have higher beta-cell response to GLP-1 infusion during a hyperglycemic clamp,²⁰⁷ but no significant differences were observed when genotypes at rs3765467 and rs761386 (an intronic variant in perfect linkage disequilibrium with the intronic short tandem repeat at rs5875654 8GA/7GA) were compared in relation to changes in plasma glucose levels after exenatide treatment. Finally, the minor (A) allele of the low-frequency rs10305492 (Ala316Thr) was associated at genome-wide level with lower fasting glucose levels,²¹⁴⁻²¹⁶ and lower risk of

T2DM, but lower early insulin secretion and higher 2-h glucose during an OGTT.²¹⁶

3.4.2 | Associations replicated in multiple studies

As anticipated in Section 3.2.1, *KCNQ1* channels are involved not only with the mechanisms of insulin secretion but also in GLP-1 and GIP release from the intestinal endocrine cells.²¹⁷ In a small pilot study, *KCNQ1* polymorphisms rs163184 G was associated with lower-HbA1c reduction in response to DPP4 inhibitors treatment,²¹⁸ consistent with previous findings in European,¹²⁵ South American,¹²⁶ and Asian^{123,124} subjects. rs2237895, rs151290, rs2237892, and rs2237897, all falling within the same intron as rs163184, were found to be associated with several OGTT-derived indexes of insulin secretion, although not during the intravenous glucose tolerance test (IVGTT), in nondiabetic subjects.²¹⁹ Regardless, nondiabetic individuals homozygous for the diabetes protective allele (A) at rs151290 exhibited lower-active GLP-1 concentrations at 10 minutes during the OGTT.²²⁰

Although *TCF7L2* (previously addressed in Section 3.2.2) has been suggested to regulate proglucagon gene expression, and thus GLP-1 synthesis in intestinal L cells,²²¹⁻²²³ no significant variation in the concentration of GLP-1 was observed in carriers of different genotypes of the risk variant rs7903146.^{220,223,224} Results reporting impaired insulin secretion in response to GLP-1 infusion rather suggested that two variants (rs7903146, rs12255372) in *TCF7L2* might reduce GLP-1 action on beta cells.^{224,225} In support of the latter theory, reduction in HbA1c in response to 24 weeks of treatment with the DPP-4 inhibitor linagliptin was reportedly attenuated in homozygous carriers of the risk allele rs7903146 T.²²⁶ Nevertheless, other studies have observed no rs7903146 attributable differences in GLP-1-induced beta-cell responsiveness.²²⁰

3.4.3 | Associations with nominal significance lacking replication (supporting information)

4 | CONCLUSIONS

Although the development of T2DM is clearly associated with a familial history of diabetes with a heritability estimated at 30%-70%,²²⁷ the current set of about 100 established susceptibility loci with robust association signals, identified primarily through large-scale GWAS, captures only 10% of familial aggregation of the disease.^{228,229} Disappointingly, although the identification of such a large number of novel susceptibility loci has opened up the opportunity to translate this genetic information into the improvement of T2DM risk prediction, the available data suggest that genetic screening is currently of little value in clinical practice with risk variants adding very little to the predictive power provided by clinical risk factors alone.²³⁰ In addition to this, we are unaware of how most of those susceptibility loci contribute to diabetes incidence, especially in the case of non-coding polymorphisms or genes that do not translate into proteins; therefore, we are yet incapable of exploiting them as drug targets for functional intervention on the disease.

Genetic investigation has also been dedicated to evaluate the interindividual variability in the response to oral and injectable glucose-lowering agents, and in recent years, many pharmacogenetic studies of associations between genetic variants and glucose-lowering drug response have been published. To a large extent, these studies were designed to identify subsets of subjects more or less likely to experience therapeutic response to the drug in question or to develop side effects. Indeed, the care of patients with T2DM requires an individualized approach because of the fact that the disease is heterogeneous, alterations in molecular and pathophysiological pathways of glucose homeostasis differ between subjects, and the variable effects of existing therapies make it difficult to predict individual response to glucose-lowering medications.²³¹ Clearly, an individualized approach is important because of the multitude of clinical features involved in decision-making including age, body weight, disease duration, life expectancy, glycemic control history, risk of hypoglycemia, adverse effects of glucose-lowering medications, presence of complications and comorbid conditions, and psycho-socio-economic factors.^{232,233} Throughout this review, it was definitely shown how ethnicity is also a major determinant of the outcomes.²³⁴⁻²³⁶ The usual approach for T2DM therapy comprises the stepwise addition of medications to lifestyle interventions, usually beginning with a single oral drug and advance to combination therapy, followed by the addition or substitution of insulin, based on the progressive failure of the medications to maintain adequate glucose control. In the context of personalized or precision medicine, pharmacogenetic information may be useful for patient stratification in order to identify responders and to balance the benefits of glucose-lowering medications with their potential risks.

Testing few genetic markers may be a relatively straightforward method to evaluate the above-mentioned biologic factors, keeping in mind that the individual genetic asset is independent from the time point of the disease course; thus, it can reveal information that would otherwise be disguised by the disease itself.

In this comprehensive review, we attempted collecting all the literature on the pharmacogenetics of diabetes medications. Although it is recognized that interindividual variability in therapeutic response is partly due to genetic heterogeneity, the pharmacogenetic studies herein reported have shown no consistent results. For instance, although there is evidence that genetic factors influence up to 34% of the glycemic response to MET,⁴ the combined effect of the *ATM* and *SLC2A2* loci on MET response has been shown to be minimal, suggesting that other genetic determinants of MET response remain to be revealed. Moreover, a recent Danish study, carried out in a population-based cohort predominantly treated with MET (55%), has investigated the influence of 48 T2DM susceptibility variants on disease progression assessed as early redemption of either a glucose-lowering drug or an insulin drug prescription. Results have shown that common T2DM-associated gene variants do not significantly affect disease progression requiring additional therapies.²³⁷

Several issues can be highlighted about the design of most of the studies evaluated for this review. It is important to note that none of the published studies was a prospective randomized clinical trial specifically conceived to unravel pharmacogenetic associations. Such approach would be able to limit selection bias and confounding

factors, especially if performed on large-scale cohorts. Instead, we collected several observational, cross-sectional, or retrospective studies, mostly with a small sample size, devoid of the discovery power required to identify smaller effect sizes. Many studies have investigated the effects of genotypes on a single-medication intervention without including a placebo or a control group. Therefore, it is not possible to exclude that these studies have reported the effect of genotype rather than the modification of the response to the medication. In addition, most studies did not address the issue of multiple comparisons, so that it is possible that the reported findings are false positives. Many associations were only assayed in a single study (supporting information), which most of the time did not include enough details to judge the rigorosity of the research. Moreover, a number of studies did not report on testing for Hardy-Weinberg proportions and on masking of genotyping personnel. Furthermore, genotyping calls obtained with probes or restriction fragment length analysis were rarely confirmed by sequencing. With few exceptions, the authors adopted the candidate gene approach, which raises the concern of selective reporting of results and publication bias. Overall, the reported effect size of genetic variants on glucose-lowering drug response is small and, in many cases, clinically meaningless.

Notably, we should always assume the presence of the “winner curse” because of the overestimation of the effect size of a newly identified genetic association, when the statistical power of the discovery study is not sufficient to detect the true OR of smaller magnitude or when positive results are reported and null results are not. As a consequence, winner curse implies that the power required to independently confirm the association will be underestimated, resulting in failure of replication. This type of bias cannot be resolved by meta-analyses since the heterogeneity of pharmacogenetic studies, by itself, precludes comparisons within outcomes and quantitative synthesis with meta-analyses. In addition to this, most findings were only confirmed in one ethnicity. Although each population with its unique genetic and social fingerprint differs from the others in allele frequencies, it would be expected that a specific, biologically supported interaction between gene and drug would be conserved across different ethnicities.

Finally, most of the studies available in the literature have only focused on the effects of a single site on drug efficacy, but researchers have already begun evaluating the joint contribution of T2DM-related loci.²³⁸

In order to account for such heterogeneity, this review groups the results in the following categories: associations at GWAS level of significance, associations replicated in multiple studies, and associations with nominal significance lacking replication. With this outline, we have been able to identify 64 genes and approximately 200 informative genetic variants. Keeping in mind the above described limitations of the studies, some reports seem to provide robust evidence to support specific, biologically plausible, gene-drug interactions. The most robust evidence seem to support a role for variants in *OCTs*, *ATM*, and *SLC2A2* loci with MET response, *CYP2C9*, *TCF7L2*, *ABCC8*, *KCNJ11* and *IRS1* loci with SUF response, *PPARG* locus with TZDs response, and *GLP1R* locus with DPP-4 inhibitors/GLP-1 receptor agonists response.

5 | FUTURE DIRECTIONS

The incorporation of pharmacogenetic information into clinical practice in the context of personalized medicine cannot occur without the results of well-designed studies proving significant gene-drug interactions. The technology of genetic investigations has reached formidable levels nowadays; commercial probe-based SNP array platforms can now genotype, with greater than 99% accuracy, about one million SNPs at the same time per individual in one assay. Next-generation sequencing can deliver the same information that SNP arrays can produce but with greater resolution and accuracy and the possibility to extend the approach from target SNPs to target genes. Furthermore, next generation sequencing can uncover structural DNA modifications that SNP arrays do not resolve. Cost-wise, the machinery required for signal detection of SNP arrays and next generation sequencing might appear impractical for immediate applications. Nevertheless, it is widely recognized that diabetes imposes an important economic burden on national healthcare system, with the most drainage deriving from hospital inpatient care after the onset of micro/macrovacular complications. An additional healthcare cost is related to the therapeutic failure of drugs as well as serious adverse side effects of drugs on individuals. It is possible then to anticipate that when the clinical practice will take advantage of the genetic information of the diabetic patients, this will provide a useful resource for the prevention of T2DM progression and the personalization of treatment enabling the identification of the precise drug that is most likely to be effective and safe for each patient, and the reduction of the economic impact on a global scale.

AUTHORS' CONTRIBUTIONS

G.C.M. and F.A. researched the literature databases, compared, and discussed each record. G.S. and G.C.M. wrote the manuscript. F.A. edited the manuscript, and G.S. revised the final version.

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CONFLICT OF INTERESTS

The authors have nothing to disclose.

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