Pharmacogenomics and Personalized Medicine

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REVIEW

Pharmacogenomics and Personalized Medicine in Type 2 Diabetes Mellitus: Potential Implications for Clinical Practice

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Abstract: Type 2 diabetes mellitus (T2DM) is the most common form of diabetes, and is rising in incidence with widespread prevalence. Multiple gene variants are associated with glucose homeostasis, complex T2DM pathogenesis, and its complications. Exploring more effective therapeutic strategies for patients with diabetes is crucial. Pharmacogenomics has made precision medicine possible by allowing for individualized drug therapy based on a patient's genetic and genomic information. T2DM is treated with various classes of oral hypoglycemic agents, such as biguanides, sulfonylureas, thiazolidinediones, meglitinides, DPP4 inhibitors, SGLT2 inhibitors, α-glucosidase inhibitors, and GLP1 analogues, which exhibit various pharmacogenetic variants. Although genomic interventions in monogenic diabetes have been implemented in clinical practice, they are still in the early stages for complex polygenic disorders, such as T2DM. Precision DM medicine has the potential to be effective in personalized therapy for those suffering from various forms of DM, such as T2DM. With recent developments in genetic techniques, the application of candidate-gene studies, large-scale genotyping investigations, genome-wide association studies, and "multiomics" studies has begun to produce results that may lead to changes in clinical practice. Enhanced knowledge of the genetic architecture of T2DM presents a bigger translational potential. This review summarizes the genetics and pathophysiology of T2DM, candidate-gene approaches, genome-wide association studies, personalized medicine, clinical relevance of pharmacogenetic variants associated with oral hypoglycemic agents, and paths toward personalized diabetology.

Keywords: pharmacogenomics, personalized medicine, type 2 diabetes, antidiabetic drugs

Introduction

Type 2 diabetes mellitus (T2DM), a complex polygenic disorder, is a major burden worldwide.[1] Genome-wide association studies (GWASs) have detected several gene variants associated with diabetes in different Indian subethnic populations. Population-specific riskalleles have been seen to increase diabetes prevalence in South Asians.[2] The worldwide prevalence of diabetes has been predicted to double from 171 million cases in 2000 to 366 million in 2030, and then to 642 million by 2040, with approximately 79.4 million by 2030 in India.[3] According to Wild et al, the "top" three countries with the most T2DM cases are India, China, and the US, with estimates of 79.4 million, 42.3 million, and 30.3 million by 2030, respectively.[4] Although diabetes is a global health concern, its burden is more evident in developing countries like India. Economically, the global encumbrance

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of diabetes is huge, with 75% prevalence in low- and middle-income countries (LMICs). India is considered the diabetes capital of the world, with a large number of diabetic subjects and individuals remaining undiagnosed, accounting for >50% of people.[3] The use of molecular testing to customize treatment widely is not yet possible. Furthermore, diabetes treatment based on a homogeneous therapeutic algorithm frequently leads to therapeutic failure with various diabetic complications.[3] With the advancement of high-throughput sequencing technologies, combined "omics" data, such as genomics, transcriptomics, proteomics, metabolomics, can be accumulated and used in global profiling of health and diseases.[4] Combined analysis of big data and routinely gathered clinical and laboratory data can be used in personalized therapeutic approaches.[5] Personalized medicine is the most promising strategy in treating a complicated polygenic illness like T2DM, because of variability in phenotypes across population groups and the need to determine the appropriate medication for each individual.[6] This new paradigm is based on the patient's genetic and metabolic structure to customize diabetes diagnostics, prevention, prognostics, and treatment. Comprehending the widespread prevalence of diabetes, personalized diabetes management is considered imperative. As such, this demands the development and implementation of a framework for personalized diabetes care. The road to personalized medicine is interesting, yet challenging. This review focuses on the current opportunities and challenges for implementation of personalized medicine in the clinical practice of T2DM management — "personalized diabetology."

Diabetes Pathogenesis and Gene Variants

GWASs have identified several gene loci involved in the various pathophysiological pathways of diabetes, explaining its complex polygenic nature.[7–9] Various gene loci are involved in insulin secretion, insulin resistance, obesity-associated diabetes, fasting glucose, β-cell count, and function. These genomic data can help in early disease prevention and selection of tailored diabetic therapy to achieve optimal glycemic control, thereby preventing or delaying the development of diabetic complications. In Figure 1, the pathogenic effects of certain T2DM-related genes in Indian populations are summarized, based on GWASs on T2DM pathogenesis in Indian subjects.[10–32]

Genetics of Type 2 Diabetes

Candidate-Gene Studies

The candidate-gene approach focuses on a population of distinct individuals, rather than related family members.

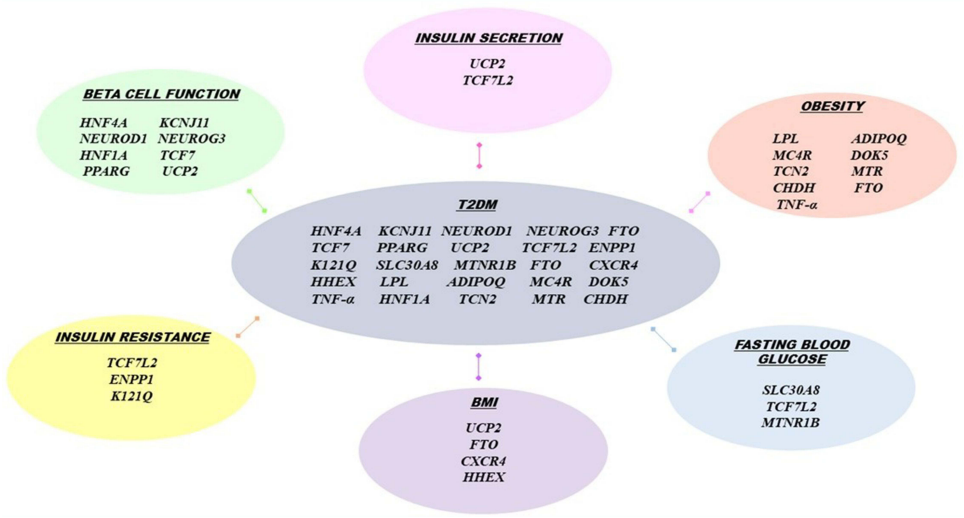

Figure 1 Pathogenic effects of certain T2DM-related genes.

Abbreviations: *HNF4A*, Hepatocyte nuclear factor 4 alpha; *KCNJ11*, Potassium Inwardly Rectifying Channel Subfamily J Member 11; *NEUROD1*, Neuronal Differentiation 1; *NEUROG3*, neurogenin 3; *HNF1A*, hepatocyte nuclear factor 1 homeobox A; *TCF7*, Transcription Factor 7; *PPARG*, Peroxisome proliferator-activated receptor gamma; *UCP2*, Uncoupling Protein 2; *TCF7L2*, Transcription factor 7-like 2; *ENPP1* K121Q, ectonucleotide pyrophosphatase/phosphodiesterase 1 K121Q; *SLC30A8*, Solute Carrier Family 30 Member 8; *MTNR1B*, Melatonin Receptor 1B; *FTO*, fat mass and obesity-associated gene; *CXCR4*, C-X-C Motif Chemokine Receptor 4; *HHEX*, Hematopoietically Expressed Homeobox; *LPL*, Lipoprotein lipase; *ADIPOQ*, Adiponectin, *C1Q* And Collagen Domain Containing; *MC4R*, melanocortin-4 receptor gene; *DOK5*, Docking Protein 5; *TCN2*, Transcobalamin 2; *MTR*, 5-Methyltetrahydrofolate-Homocysteine Methyltransferase; *CHDH*, Choline Dehydrogenase; *TNF-α*, Tumor necrosis factor -α.

These studies are theory-motivated,[1] analyzing gene variants within functional candidate genes based on data generated by linkage studies regarding genetic association. Though novel genes cannot be identified,[1] these studies signify as the most influential method. Intensive sequencing of genes thought to be involved in T2DM pathogenesis like glucose metabolism, insulin secretion, and insulin resistance is done in candidate genetic analysis.[33] Along with the assistance of data from the Human Genome Project, which includes a public database of single-nucleotide polymorphisms (SNPs), candidate genetic variants are detected.

PPARG

An initial candidate gene positively associated with T2DM was *PPARG* of the nuclear hormone–receptor family, regulating transcription.[1] As a molecular target for the antidiabetic-drug class thiazolidinediones, this makes it a promising candidate gene.[34] Substitution of proline for alanine at position 12 in this protein, ie, polymorphism Pro12Ala (rs1801282), in *PPARG2* on extra exon B has been observed to yield a 20% higher risk of diabetes.[33] The genetic variant in this gene has been found to have high correlation with elevated transcriptional function, and an elevated function of defense against T2DM.[35]

KCNJ11

KCNJ11 is an inwardly rectifying potassium channel (subfamily J, member 11) encoding Kir6.2. It is an ATP-sensitive channel, coding for four subunits.[34] It acts as a significant gene in regulation of insulin secretion by β cells,[33] where polymorphisms lead to elevated K-ATP channel function, causing β-cell dysfunction.[36] In 1998, a missense polymorphism in *KCNJ11* E23K was initially identified to be related to T2DM and confirmed by various studies, including GWASs.[37] *KCNJ11* is associated with neonatal diabetes as well, and its rare potential polymorphism can even lead to a permanent form of neonatal diabetes.[38]

IRS1 and *IRS2*

Insulin Receptor Substrate 1 and Insulin Receptor Substrate 2 (*IRS1* and *IRS2)* play a crucial role in the insulin-signaling cascade,[39] and polymorphisms in these genes have been found to be linked with reduced insulin sensitivity.[40]

WFS1

The missense mutation rs734312 is found in exon 8 of Wolfarin ER Transmembrane Glycoprotein (*WFS1)*. Also, elevated oral glucose-tolerance test–derived insulin-secretion levels are related to variant rs10010131. These two polymorphisms in have been found to have substantial defensive action against T2DM.[41] SNPs in *WFS1* have strong associations with T2DM.

HNF1A, *HNF1B*, and *HNF4A*

HNF1A, *HNF1B*, and *HNF4A* are significantly associated with monogenetic diabetes in the young, also called maturity-onset diabetes of the young.[33] The 127L, A98V, and S487N variants in *HNF1A* mutation have decreased transcription function in genes engaged in GLUT2 mechanisms. Polymorphisms of *HNF1A* like AG8V and S487N are highly developed in late-onset autosomal-dominant DM, which is clinically similar to T2DM.[42]

ENPP1

ENPP1 is associated with T2DM.[43] The missense variant rs1044498 of the *ENPP1* K121Q polymorphism is associated with T2DM and the development of insulin resistance, which was also supported by various other studies in distinct populations.[44] A meta-analysis on 11,855 Chinese subjects established that the Q allele of K121Q gene may act as a predisposing factor of T2DM, augmenting T2DM susceptibility.[45] However, no association has been replicated in other studies on different populations such as a one involving north Indian subjects, which reported no associations among *ENPP1* K121 polymorphisms, T2DM, and related quantitative metabolic traits.[46]

Genome-Wide Association Studies

The Human Genome Project, completed in 2003, mapped the entire human genome.[47] This has led to subsequent developments in genomic research. The international haplotype map (HapMap) project primarily sequenced 3.9 million SNPs in 270 DNA samples from four distinct ethnic populations, followed by detection of millions of SNPs, which got stored on a public database.[48] Another international research effort, the 1000 Genome Project, has also detected SNPs throughout the human genome and added data, and is used widely by the research community. Utilization of these data sources and enhancement of advanced high-throughput sequencing technology thus play an important role in studying various T2DM-associated genes and in comprehending the disease at its

genetic level. A French cohort study involving 661 T2DM cases and 614 controls that covered 3,92,935 SNP loci was the first GWAS to identify novel genetic variants like *SLC30A8*, *HHEX*, *EXT2*, and *COC387761* as being associated with T2DM.[49] GWASs have illustrated novel pathways, pointed toward fundamental biology, confirmed prior epidemiological observations, drawn attention to the role of β-cell dysfunction in T2DM, explained ~10% of disease heritability, tempered our expectations with regard to their use in clinical prediction, and provided possible targets for pharmacotherapy and pharmacogenetic clinical trials. GWASs have also been integrated with high-throughput metabolomic profiling to provide scientific insights into how genetic diversity influences metabolism and how metabolic differences in plasma might help identify important genes within chromosomal areas associated with T2DM.[50]

Personalized Medicine: A Paradigm Shift in Diabetes Treatment

Applying data generated from various clinical trials on the genetics of diabetes involving subjects who are usually young with few or no comorbid diseases to the general diabetic population remains a challenge. Even with data produced from individuals meeting selective inclusion criteria of glycemic control and development of complications, replicating this evidence-based medicine for diabetic patients of various heterogeneity may not always provide a similar outcome. Sometimes, it even leads to adverse outcomes. With diverse genetic variants studied in GWASs, linkage with different diabetic risks and pathogenesis mechanisms like insulin secretion and resistance, glucose homeostasis, and membrane transportation necessitates personalized medicine in diabetes management.[51]

In complex polygenic disorders like T2DM, early risk prediction and prevention are essential. Various randomized controlled trials have established that the risk of developing diabetes can be reduced by half if predicted early. Personalized medicine can play a potential role, enabling clinicians to provide tailored therapy.[52] In addition to clinical markers like phenotypic characteristics and markers of metabolism, endothelial dysfunction markers, data on well-established genetic variants associated with T2DM risk possess great significance in diabetic prevention. Genetic variants in *TCF7L2*, *PPARG*, *KCNJ11*, *WFS1*, *SLC30A8*, *JAZF1*, and *HNF1B* have been established as posing a high risk of developing T2DM.[28] Therefore, the use of big data generated by GWASs and other "multiomics," including proteomics, metabolomics, and transcriptomics, along with advanced high-throughput sequencing technologies, will provide a promising future in precision medicine for diabetes. Although, genetic testing regarding the monogenic form of diabetes is available as a tool in specialized diabetes clinics, the use of precision medicine for the polygenic form of diabetes has not yet evolved. Incorporating omics data with clinical phenotype data of a patient potentially aids in better risk prediction, prevention, and management of T2DM. A recent data-driven cluster analysis of six diabetes-related variables in newly diagnosed diabetes patients from the Swedish All New Diabetics in Scania cohort (n=8,980) has been replicated in three other cohorts: the Scania Diabetes Registry (n=1,466), All New Diabetics in Uppsala (n=844), and Diabetes Registry Vaasa (n=3,485). Five clusters of diabetic patients with distinct disease characteristics and a higher risk of diabetic complications were identified, each with a different genetic association from conventional T2DM. As a result, such subcategorization aided in a better understanding of diabetes stage and pathogenesis, allowing for targeted and early intervention. This new substratification might eventually help to tailor and target early treatment for patients who would benefit most, thereby representing a first step toward precision medicine in diabetes.[53]

Deep-learning algorithms, which can detect exceedingly complex patterns in huge data sets, have been shown to be effective in illness-prediction models and biological process prediction.[54] These findings demonstrate that a multiomics technique provides additional information for T2DM prediction and treatment management. In the near future, deep-learning algorithms may be applied in multiomics studies on T2DM, as well as precision medicine. The development of systems biology methods for the integration of multiomics data is crucial for forecasting rising fasting plasma-glucose levels. SNPs in such genes as *RPL7AP27*, *SNX30*, *SLC39A12*, and *BACE2* have been found to be highly associated with increased fasting plasma-glucose levels.[55] This demonstrates that combining candidate SNPs with IgG glycomics can yield T2DM-biomarker potential. The strong predictive potential observed by integrating genomes and glycomic biomarkers suggests that such multiomic approaches could be used to provide predictive, preventive, and personalized T2DM medication.

Effect of Pharmacogenetics on Antidiabetic Medications

Pharmacogenomics means formulating a genetically tailored therapeutic plan to achieve the best optimal individual response. The individual's genetic profile is considered to optimize pharmacokinetics and pharmacodynamics, in achieving the desired drug efficacy and response. In the recent years, several gene polymorphisms on the therapeutic response of various anti-diabetic drugs have been studied. However, issues like lack of knowledge on clinical relevance and implementation, lack of structured guidelines and ethical, social, technological, legislative, and economic issues remains a challenge. Therefore, giving importance to interindividual genetic variability in response to antidiabetic agents is the primary factor in achieving "personalized diabetology".

Metformin

ATM

A meta-analysis of three cohort studies — Hoorn Diabetes Care System (DCS) cohort,[56] CARDS cohort,[57] and smaller Rotterdam Study cohort[58] — concluded that the *ATM*, a member of the PI3K family and important for cell-cycle control and DNA repair, in which rs11212617 polymorphism was associated with metformin-treatment response.[59] This polymorphism and rs628031 of *SLC22A1* were found to have no association with metformin treatment in an Iranian T2DM population.[60] In a Caucasian population, rs11212617 had a significant association with metformin response, with low plasma concentration of metformin indicating high cellular-level action.[61] However, in a south Indian population, these SNPs were found to have no contribution to T2DM incidence.[62]

OCT1

The allele and genotypes of the *SLC22A1* rs622342 polymorphism were associated with metformin effectiveness in south Indian patients with T2DM.[63] The GoDART database study examined rs122083571 and rs72552763 in 2,216 participants and reported that patients with these polymorphisms on *OCT1* inhibitors had more than fourfold the risk of acquiring intolerance to metformin (OR 4.13, 95% CI 2.09–8.16; $P<0.001$).[64] The rs2297374 polymorphism (+43C>T) and metformin response showed no significant association in Indian populations,[65] and 20% frequency of rs2282143 (1022C>T) was detected in Indian subjects. The influence of rs1867351 (156T>C) on metformin-action regulation has been examined in an Indian population, showing a frequency of 27% (2018).[66] A study on a Mexican population recently identified CC-rs622342 (β=1.36, $P<0.001$), AA-rs628031 (β=0.98, P=0.032), and GG-rs594709 (β=1.21, P=0.016) in the *SLC22A1* gene to be associated with reduced metformin effectiveness, with increased HbA_{1c} levels.[67] The variants R61C (rs12208357), G401S (rs34130495), G456R (rs34059508), and 420del (rs72552763) were associated with reduced metformin activity.[68]

OCT2

Genetic variants in the *SCL22A2* gene encoding the OCT2 protein, such as T199I, T201M, and A270S, have been fouund to be related to decreased metformin function.[69] However, no significant association between *SLC22A2* SNPs (rs10755577, rs17588242, rs17589858, rs2928035, rs312024, rs312025, rs312026, rs3127573, rs533452, and rs662301) and metformin clearance has been found in healthy Caucasian males.[70] A recent study also failed to replicate associations between any SNPs of *SLC22A2* and glucose regulation. However, using multinomial logistic regression and adjusting for covariates like age and BMI, associations between glucose regulation and SNPs within *SLC22A1*, *SLC22A2*, and *SLC22A3* were replicated.[71]

OCT3

The four *SLC22A3* SNPs (rs12194182, rs2292334, rs2504927, and rs3123634) have been found to have no association with metformin action in Caucasians.[71] The rs2292334 and rs12194182 SNPs are associated with lower risk of T2DM and lower mean HbA_{1c} levels. In an Iranian study, metformin showed better glucose regulation and lipid management, irrespective of OCT3-564G>A variant.[72] The genetic variants in *PRPF31*, *CPA6*, and *STAT3* are associated with novel glucose-lowering mechanisms for metformin.[73] A significant association was observed in a recent study in 2019 on T2DM patients between *TCF7L2* rs7903146 and metformin response.[74] Carriers of the G allele of the intronic SNP rs3889348 exhibit significantly lower expression of *SLC29A4*, which encodes PMAT. Since it aids in metformin absorption, metformin therapy increases the risk of gastrointestinal intolerance.[75]

Sulfonylureas

Sulfonylureas are metabolized in the liver primarily by the polymorphic cytochrome P450 isoenzyme 2C9, encoded

by *CYP2C9*. In a large GoDARTS[64] retrospective study of 1,073 subjects, carriers of loss-of-function *CYP2C9**2 or *CYP2C9**3 alleles had 3.4-fold the higher probability of attaining glycemic control of carriers of the wild-type alleles. Two polymorphisms — *CYP2C9*2* (I359L) and *CYP2C9*3* (R114C) — were associated with elevated serum-sulfonylurea levels.[76]

Sulfonylureas are insulin secretagogues that bind the SUR1 subunit (encoded by *ABCC8*), play a major role in insulin secretion, and are potential candidate for T2DM. The 3c → t polymorphism and the Thr759Thr (ACC → ACT) silent polymorphism were initially associated with T2DM in Caucasians.[77] A genotyping study assessing this polymorphism failed to replicate this in a south Indian population of 637 diabetes patients.[78] The *KCJN11* E23K variant is associated with T2DM and sulfonylurea efficacy in Caucasians.[79] In Caucasian T2DM patients, rs7903146 and rs1801278 polymorphisms of the *TCF7L2* and *IRS1* genes are associated with poor sulfonylurea response.[80] In an Indian study involving a Gujarat population of T2DM patients, genetic variation at rs12255372 was associated with the sulfonylurea effectiveness.[81] Several genetic variants of *TCF7L2* are related to T2DM in diverse ethnicities, among which rs7903146 (intron 4) has the strongest association with T2DM, while rs12255372 and rs7903146 are related to poor therapeutic outcomes.[82,83] *MIR4532* rs60452575 influenced *KCNJ11* expression and sulfonylurea effectiveness in a Chinese population.[84]

DPP4 Inhibitors and GLP1 Analogues

DPP4 inactivates the incretins GLP1 and gastric inhibitory polypeptide (GIP). DPP4 inhibitors extend the half-life of these incretins, and this is correlated with augmented insulin release and reduced glucagon release.[85] GLP1-receptor agonists and DPP4 inhibitors control blood glucose by targeting the body's incretin system. GLP1 agonists act as "incretin mimetics" and DPP4 inhibitors prevent the breakdown of endogenous incretin. DPP4 inhibitors and GLP1-receptor agonists are recommended as second-line glucose-lowering agents by the American Diabetes Association and the European Association for the Study of Diabetes in cases where patients require combination therapy for adequate glycemic control or when metformin or sulfonylureas are ineffective.[86,87] The first DPP4-selective inhibitor was sitagliptin, which was followed by vildagliptin, saxagliptin, linagliptin, and most recently alogliptin. Exenatide, liraglutide, lixisenatide, dulaglutide, and albiglutide are the five GLP1-receptor agonists currently approved for the treatment of T2D.[88]

In a recent study on a Central European population of 206 T2DM patients, missense variant rs6923761 in the *GLP1R* gene was associated with lower glucose control in 6-month exposure to gliptins.[89] In individuals with high body fat, *DPP4* rs6741949 in intron 2 position showed negative correlations with insulin secretion (P=0.0061), glucose tolerance (P=0.0208), and glucose-stimulated GLP1 levels (P=0.0229).[90] The rs2285676 variant in the *KCNJ11* gene is a predictor of the therapeutic effect of DPP4 inhibitors.[91] In a study on 137 Caucasian diabetics, the *KCNQ1* rs163184 T>G variant was related to glucose regulation of DPP4 inhibitors.[92] Variants of *CDKAL1* (rs7754840 and rs7756992) in Japanese are linked with glycemic control activity of DPP4 inhibitors.[93] In the Taiwanese, rs57803087 in *PRKD1* is highly associated with DPP4-inhibitor function.[94] GLP1-analogue drugs are incretin mimetic agents. The SNP rs7202877 has been found to control the expression of *CTRB1* and *CTRB2* for chymotrypsin, a significant regulator of the incretin mechanism in non-T2DM patients.[95] In a recent study, T2DM patients with minor A allele of *GLP1R* (rs6923761), who had received exenatide or liraglutide showed a more significant delay in gastric emptying $T_{½}$ to baseline.[96] Although *TCF7L2* (rs7903146) and *WFS1* (rs10010131) and *KCNQ1* (rs151290, rs2237892, and rs2237895) were initially shown to be related to GLP1 response, another study of the effect of these variants on GLP1 concentrations showed no association in healthy individuals. Also, *GLP1R* polymorphisms showed no statistical association with GLP1-analogue responses in T2DM patients with poor glycemic control.[97]

Sodium–Glucose Cotransporter 2 Inhibitors

SGLT2 is encoded by the *SLC5A2* gene, located on human chromosome 16p11.2. From genotyping of five SNPs in *SLC5A2* gene locus in 603 T2DM subjects, no association between *SLC5A2* variants and empagliflozin response was detected.[98] On the other hand, the rs9934336 G allele has been found to be associated with increased 30-minute plasma glucose, 120-minute insulin concentrations, and AUC_{120} glucose on oral glucose-tolerance test in 907 nondiabetic Sorbs (P<0.05).[99] In addition, the *UGT1A9*3* and *UGT2B4*2* polymorphisms have been

demonstrated to increase plasma concentration of the SGLT2 inhibitor canagliflozin in carriers of wild-type alleles.[100] Kan et al investigated the effect of alogliptin on liver function and glucose regulation in T2DM patients with nonalcoholic fatty-liver disease and *PNPLA3* rs738409 C>G genotypes. Those with the G allele showed a positive relationship between improved HbA_{1c} levels and alterations in liver-transaminase levels.[101]

α-Glucosidase Inhibitors

The STOP-NIDDM trial,[102] with 770 study subjects, studied the acarbose response and its association with genetic variants of *PPARA*, *HNF4A*, *LIPC*, *PPARG2*, and *PPARGC1A* were studied. Findings were not replicated in other populations with preexisting T2DM. The Pro12Pro genotype of *PPARG2* gene and the 482Ser allele of *PPARGC1A* has been established to be associated with the transformation of impaired glucose tolerance in T2DM. Acarbose averts the progression of diabetes, irrespective of *PPARG2* genotype.[103]

Meglitinide

SLCO1B1, *CYP2C8*, *CYP3A4*, *TCF7L2*, *SLC30A8*, *IGF2BP2*, *KCNJ11*, *KCNQ1*, *UCP2*, *NAMPT*, *MDR1*, *PAX4*, and *NEUROD1* were found to be associated with meglitinide response in the Chinese population.[104] OATP1B1, which *SLCO1B1* encodes, facilitates hepatic transport of the drug. Genetic polymorphisms in *CYP2C8* and *CYP2C8**1/*3 genotypes are associated with reduced plasma concentrations of repaglinide.[105] In a study on Chinese T2DM patients on repaglinide, the *NAMPT* −3186C/T polymorphism affected plasma levels of postprandial serum insulin and total cholesterol levels.[106] The *KCNQ1* rs2237892 T and rs2237895 C alleles respond to repaglinide positively.[107] As *KCNQ1* plays a vital role in controlling insulin resistance through the IRS2–PI3K–Akt signaling pathway, the genetic polymorphism in this gene has been found to affect repaglinide response in the same population.[107] The frequency of the *ABCC8* rs1801261 allele has been found to be higher in T2DM patients than control subjects (22.6% vs 11%, $P<0.01$), exerting effects on repaglinide response.[108] The C/C homozygotes of the *ABCC8* exon16– 3T/C variant have shown better repaglinide response in insulin sensitivity than the T/C and T/T genotypes of the *KCNJ11* E23K variant.[109]

Thiazolidinediones

Thiazolidinediones are PPAR activators that decrease circulating free fatty acids, thereby enhancing sensitivity to insulin and reducing hyperglycemic episodes.[110] The rs296766 T allele of *AQP2* and rs12904216 G of *SLC12A1* have been found to be associated with edema in rosiglitazone users.[111] *PPARGC1A* Thr394Thr and Gly482Ser polymorphisms are associated with rosiglitazone action in Chinese patients with T2DM.[112] The P12A variant in *PPARG* is associated with lowered rosiglitazone effectiveness.[113] Another Asian study with 250 patients demonstrated that carriers of the minor allele of variant rs1801282 in *PPARG* had higher odds of being responders to pioglitazone than carriers of wild-type alleles.[114] Additionally, carriers of the A allele of rs6467136 in *PAX4* showed improved response to rosiglitazone.[115] The major metabolizer of thiazolidinedione is CYP2C8, in which the *3 variant[116] has reduced response to insulin, with lower plasma concentration of rosiglitazone.[117] The transporter OATP1B1, encoded by *SLCO1B1*, facilitates hepatic uptake of thiazolidinediones, which are metabolized by the enzyme CYP2C8 (encoded by *CYP2C8*), are associated with two variants — Val174Ala and rs4149056 — in the Scottish population.[116] Genetic variants associated with therapeutic responses to antidiabetic medications are summarized in Table 1.

Current Perspectives and Future Prospects of Personalized Medicine in Type 2 Diabetes

The Precision Medicine in Diabetes Initiative was launched in 2018 by the American Diabetes Association in collaboration with the European Association for the Study of Diabetes and the US National Institute of Diabetes and Digestive and Kidney Diseases.[118] Although the application of precision medicine in monogenic diabetes was successful, it is challenging to implement in T2DM, a complex multifactorial polygenic disease.

Over the years, more than 100 T2DM-susceptibility loci have been detected. However, the understanding of functions of these detected genetic variants in diabetic pathogenesis remains challenging. As the effect of causal variants in T2DM is small, it becomes hard to establish their association. This issue can be reduced using biobanks, which help in the accessibility of well-organized,

Table 1 Genetic Variants that Influence Antidiabetic-Medication Response

	Gene	dbSNP ID	Study Population/ Country	Main Outcome	Reference
Metformin	*ATM*	rs11212617	Netherlands	Carriers of A allele of *ATM* rs11212617 had less response to metformin than C-allele carriers.	van der Heijden et al[56]
	ATM	rs11212617	Caucasian	Carriers of minor allele of rs11212617 had lower metformin plasma concentration and hence metformin response.	van Leeuwen et al[59]
	SLC22A1	rs622342	South Indian	The rs622342 polymorphism of *SLC22A1* was associated with the therapeutic efficacy of metformin.	Umamaheswaran et al[63]
	OCT1	rs122083571 rs72552763	GoDARTS database	Carriers of these polymorphisms and OCT1 inhibitors had four times the risk of developing intolerance to metformin.	Dujic et al[64]
	SLC22A1	rs622342 rs628031 rs594709	Mexican	Carriers of these genotypes showed less response, with increased levels of HbA_{1c} after 12 months of metformin therapy.	Reséndiz-Abarca et al[67]
	SLC47A1	rs2289669	Rotterdam Cohort Study	Carriers of minor A allele at rs2289669 showed 0.3% higher HbA_{1C} reduction.	Becker et al[69]
	SLC22A3	rs12194182	Jordanian	Carriers of CC genotype exhibited the lowest mean HbA1c levels, while patients with the CT and TT genotypes exhibited higher levels.	Al-Eitan et al[71]
	PRPF31	rs254271	ACCORD trial (US and Canada)	Carriers of C allele of rs254271, an intronic variant in *PRPF31*, showed inferior metformin response.	Rotroff et al[73]
	TCF7L2	rs7903146	Bosnia and Herzegovina	Newly diagnosed patients carrying the T allele had lower insulin resistance and better glycemic response within the first year of metformin treatment.	Dujic et al[74]
Sulfonylureas	*CYP2C9*	rs1057910	Netherlands	Polymorphism of CYP2C9*3 required lowered dose of tolbutamide to regulate serum glucose.	Becker et al[76]
	KCJN11	rs5219	Central European Caucasian	Carriers of the *KCNJ11* K-allele polymorphism had greater therapeutic response to gliclazide.	Javorsky et al[79]
	TCF7L2	rs12255372	Indian	Carriers of GG genotype showed better response to sulfonylureas than GT or TT carriers.	Dhawan et al[81]
	KCNJ11	rs60452575	China	*MIR4532* rs60452575 variant influenced *KCNJ11* expression and increased sulfonylurea efficacy.	Chen et al[84]
DPP4 inhibitors	*GLP1R*	rs6923761	Slovakia and the Czech Republic	Associated with reduced glycemic response to 6-month DPP4-inhibitor therapy.	Urgeová et al[89]
	KCNJ11	rs2285676	Malaysia	*KCNJ11* rs2285676 was found to be a predictor of DPP4 inhibitor–treatment response.	Jamaluddin et al[91]
	KCNQ1	rs163184	Caucasian	The *KCNQ1* rs163184 T>G variant was associated with decreased glycemic response to DPP4 inhibitors.	Gotthardová et al[92]
	CDKAL1	rs7754840 rs7756992	Japan	*CDKAL1* was linked with glycemic control activity of DPP4 inhibitors.	Osada et al[93]
	PRKD1	rs57803087	Taiwan	*PRKD1* gene of SNP rs57803087 had a strong association with DPP4-inhibitor response.	Liao et al[94]

(*Continued*)

Table 1 (Continued).

	Gene	dbSNP ID	Study Population/ Country	Main Outcome	Reference
α-Glucosidase inhibitors (AGIs)	*PPARγ2* *PGC-1α*	Pro12Pro 482Ser	STOP-NIDDM trial subjects	*PPARG* genotypewith acarbose prevented the development of diabetes.	Andrulionytè et al[99]
				Carriers of the 482Ser allele of the *PPARGC1A* gene were responsive to acarbose treatment.	
GLP1	*GLP1R*	rs6923761	US	Carriers of A allele of *GLP1R* rs6923761 had a greater delay in gastric emptying in response to treatment with GLP1 agonists.	Chedid et al[102]
Meglitinide	*KCNQ1*	rs2237892 rs2237895	Chinese	Carriers of rs2237892 T and rs2237895 C alleles were more likely to have a positive response to repaglinide than those with rs2237892 CC and rs2237895 AA genotypes.	Dai et al[107]
	NOS1AP	rs12742393	Chinese	Carriers of risk C allele of *NOS1AP* rs12742393 may have poor therapeutic response to repaglinide.	Wang et al[108]
	ABCC8	rs1801261	Chinese	Carriers of genotype CT showed a significantly reduced response to repaglinide than those with genotype CC.	Zhou et al[109]
Thiazolidinediones	*PAX4*	rs6467136	Chinese	Carriers of the A allele showed improved response to rosiglitazone.	Chen et al[115]

Abbreviations: *ATM*, Ataxia Telangiectasia Mutated; *SLC22A1*, Solute carrier family 22 member 1; *OCT1*, Organic Cation Transporter 1; *SLC47A1*, Solute carrier family 47 member 1; *SLC22A3*, Solute carrier family 22 member 3; *PRPF31*, Pre-MRNA Processing Factor 31; *TCF7L2*, Transcription factor 7-like 2; *KCJN11*, Potassium Inwardly Rectifying Channel Subfamily J Member 11; *GLP1R*, glucagon-like peptide 1 receptors; *KCNQ1*, Potassium Voltage-Gated Channel Subfamily Q Member 1; *CDKAL1*, Cdk5 regulatory associated protein 1-like 1; *PRKD1*, Protein Kinase D1; *PPARγ2*, Peroxisome proliferator-activated receptor gamma 2; *PGC-1α*, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; *NOS1AP*, Nitric Oxide Synthase 1 Adaptor Protein; *ABCC8*, ATP Binding Cassette Subfamily C Member 8; *PAX4*, Paired box gene 4.

multiuser, large-cohort databases covering clinical, laboratory, and molecular information from large patient samples. The DNA Technology Regulation Bill 2019 in India provides for the establishment of DNA data banks at national and regional levels. There are now 336 million people with diabetes living in LMICs,[3] accounting for four in five people worldwide with diabetes. India, an LMIC that is a major epicenter of diabetes, is a diverse country with nearly 4,000 population groups and characterized by unique genetic variations within the subpopulations. GWASs involving a larger population of different ethnicities may lead to identification of more genetic loci associated with T2DM. They also may aid in the interpretation of the function and role of predetected genetic variants. This can be achieved as the cost of sequencing technologies reduces over time.

Establishing a set of biomarkers that would accurately associate with various stages of diabetes and complications is crucial. As molecular sequencing studies keep generating pharmacogenetic markers, clinical trials involving interventional therapies that target these should be conducted to ensure the reliability of the established data. One of the best examples of how precision medicine can be successfully exploited is sulfonylureas targeting the *KCNJ11* genetic variation. Metformin has been observed to enhance the antitumor activity of MEK inhibitors in human LKB1 wild-type non–small cell lung cancer (NSCLC) cell lines, regardless of *KRAS*-mutation status, by downregulating GLI1 and decreasing NF-kB (p65)-mediated transcription of MMP2 and MMP9.[119] The METAL trial was designed to determine the maximum tolerated dose and evaluate the safety and activity of metformin coupled with erlotinib in second-line treatment of patients with stage IV NSCLC whose tumors expressed the wild-type *EGFR* gene.[120] A recent multicenter clinical trial on diabetic kidney disease called Nephropathy in Diabetes Type 2 compared standard of care (n=188) with multifactorial intensive therapy (n=207) in which comprehensive therapy for the main risk factors was far more effective than standard of care in preventing major fatal/nonfatal cardiovascular events in diabetic kidney-disease patients, and its use at an early stage offered prolonged protection. As a result, such an integrated and multifactorial approach may result in better diabetic outcomes.[121] Sharing those trial results is crucial in providing new insights. Databases have been developed in recent years through sharing of data, such as the Human Gene Mutation Database[122] and ClinVar.[123]

The ancillary effects of antiglycemic drugs can also be tailored and directed toward beneficial results. In major

randomized clinical trials and real-world observational studies, SGLT2 inhibitors have shown positive pleiotropic effects on body weight, systolic blood pressure, and eGFR levels, as well as improved cardiovascular outcomes. These pleiotropic effects are advantageous for the prevention or decrease of macro- and microvascular problems, and may be especially beneficial in patients with diabetes or at risk of diabetes complications, such as CVD, HF, and CKD. This enables physicians to choose appropriate glycemic therapy based on cardiovascular and renal comorbidities.[124,125]

Electronic health-care records across health-care systems are crucial in implementing of precision medicine for diabetes, as they are easy to access and share among various systems across a wide region. Collaborations among various research societies, health-care organizations, funding organization, suppliers, and governing agencies to implement precision medicine in diabetes diagnostics, prevention, monitoring, prognostics, and treatment are crucial. It is essential to form an active network of stakeholders with patient representatives and public organizations to raise agendas and funds.

Although diabetes precision medicine involving sequencing technologies is more expensive than conventional treatment, precision medicine in monogenic diabetes has been established to be cost-effective. As diabetic complications are the primary factor in treatment expenses, early diagnosis, prevention, and intervention based on genetic variants through precision medicine may be motivation for acceptance. A critical evaluation of the cost versus benefit of sequencing technologies, genomics, and biomarkers is necessary to advocate its use in clinical practices in certain populations. The use of technology in diabetes, such as wearable glucose-monitoring sensors with minimal invasion and uninterrupted glucose measuring, is highly encouraged and practiced in various health-care systems, the best example of extensive personalized medicine in diabetes.[126]

Algorithms and guidelines on personalized diabetes therapy based on genotype should be developed based on the clinical evidence generated, aiding in implementing such evidence at the clinical level. The exploitation of artificial intelligence in clinical decision-making for an optimal therapeutic regimen for many patients will be the revolutionizing approach in personalized medicine of diabetes. Educational programs are required to train and educate clinicians, geneticists, and other health-care professionals in implementing personalized medicine for diabetes at the patient level and handling potential accidental findings, such as unexpected germ-line mutations. Adequate training of the genomic workforce can be achieved by procuring suitable funds for providing genomic education. The participation of regulatory bodies in the initial phases of precision-medicine development in diabetes is crucial for its effective execution and practice.

Individual genetic variation identification and knowledge of its role in the predisposition and pathogenesis of T2D would be a significant step in disease management, improving clinical conditions and preventing complications. In this review, we have identified the current state of genetic risk variants linked with T2DM and shown the importance pharmacogenomic studies have in associating actionable relationships between genetic and pharmacological treatments. Personalized medicine can lead to more effective drug therapy with better patient adherence in routine clinical practice. Precision DM medicine is already being used to treat monogenic forms, such as maturity-onset diabetes of the young, neonatal DM, and congenital hyperinsulinemic hypoglycemia. Precision DM medicine promises to be useful in customized therapy for those suffering from different types of diabetes, such as T2DM.[127]

T2DM is a polygenic condition, and the clinical phenotype reflects both genetic and environmental effects, making it far more challenging to define subgroups using molecular testing.[128] One strategy for precision medicine in T2DM is to divide patients into subgroups based on treatment response and then examine the biological underpinnings of each subgroup utilizing next-generation sequencing platforms and gene arrays.[129] Big data, or the growing availability of genetic and electronic health data from large populations, is a significant tool for delivering precision treatment for T2DM.[130,131]

Conclusion

The increasing incidence of diabetes is causing rising health-care costs, morbidity, mortality, and diabetes-related comorbidities. Numerous genomic technologies have led to the identification of several genetic loci associated with T2DM. However, the complete landscape of T2DM-susceptibility gene variants remains inadequate, calling for more genetic studies on various ethnicities. Moreover, it is also imperative to replicate studies on the identified gene variants through advanced sequencing technologies on different populations and subethnic groups to establish more compelling data for clinical translation. Although genomic interventions in monogenic diabetes are translated into clinical practice, they are still evolving in complex polygenic diseases like T2DM. Paradigm shifts

in the future of diabetes management are crucial in tackling the diabetes epidemic. With diverse phenotypic and genotypic features in T2DM populations, the "one size fits all" approach is inept. Comprehensive phenotyping and genotyping of diabetic individuals at the prediabetic stage helps in precision diagnostics, prevention, prognostics, and therapy. Health-care professionals can use electronic medical records consisting of individuals complete omics data, including genomics, proteomics, metabolomics, and transcriptomics. Then, decisions on therapeutic optimization can be made using potential actionable findings generated in T2DM individuals. Given the remarkable advancements made over the recent decades, it is reasonable to forecast the acceptance of "personalized diabetology" in T2DM in coming years. Recent breakthroughs in genetic techniques, the application of candidate-gene studies, large-scale genotyping investigations, and GWASs have begun to produce suggestive results that may lead to changes in clinical practice. Pharmacogenetic research has already begun to deliver on the promise of personalized diabetes treatment for some monogenic forms. The recently introduced "miRNA pharmacogenomics," which examines polymorphisms in the miRNA regulatory pathway and their relationship to drug response, would also be valuable for personalized medicine.

Author Contributions

All authors made a significant contribution to the work reported, such as conception and design, acquisition of data, analysis and interpretation of data, and drafting the article or revising it critically for important intellectual content, have agreed to submit to the current journal, gave final approval to the version to be published, and agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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