Genetic Susceptibility to Type 2 Diabetes and Implications for Therapy

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Abstract

Prevalence of type 2 diabetes is increasing rapidly around globe and effecting not only health of individuals but also socially and economically. It is a multi-factorial, polygenic metabolic disorder involving complex interaction of both genetic and environmental factors and it is characterized by increased glucose level in blood due to deficiency in insulin secretion. Recent advent of genome-wide association studies has improved the knowledge of genetic factors involved in disease progression, pathogenesis and paving way to better understand the complex pathways. These genetic variants change the drug response in patients thus making it difficult to maintain optimal glycemic levels. The genome-wide association studies are providing great insight into pharmacogenomics by revealing various new variants that effect drug response and development of personalized medication in future.

Introduction

Diabetes mellitus is a chronic condition characterized by increased glucose level due to absence/insufficient insulin secretion (Figure 1). The old classification of diabetes divided it into juvenile- and maturity-onset diabetes. Now an etiology based classification devised by the American Diabetes Association (ADA) and the World Health Organization (WHO) is used that divides diabetes into: type 1 diabetes (T1DM), type 2 diabetes (T2DM), monogenic diabetes, gestational diabetes, and other types of diabetes. Monogenic diabetes is a term used for the type of diabetes that is caused by mutation in single gene. But T1DM and T2DM are the major types of diabetes. T2DM, previously known as non–insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, is a metabolic disorder that is extremely heterogeneous multi-factorial disease and involves complex interaction of environmental factors and susceptibility genes (Figure 2). Genetic factor is one of the important risk factor.

Mode of inheritance of T2DM is polygenic i.e. polymorphism in many genes result in disease development. Type 2 diabetes may be maturity-onset diabetes of youth (MODY) 5-10% patients, latent adult-onset autoimmune diabetes (LADA) 5-10% patients, secondary
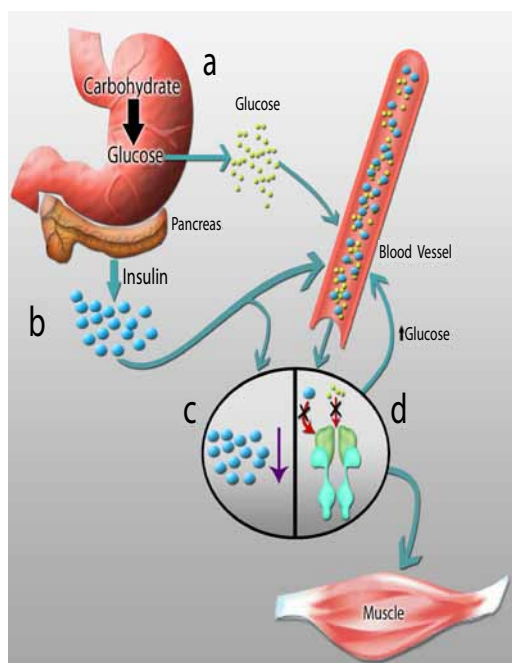

Figure 1: Overview of type 2 diabetes mellitus (T2DM).

a) Carbohydrates, metabolized to glucose in digestive tract, are released into blood stream b) stimulating the pancreas to produces insulin c). With insulin resistance, either the production of insulin decreases or it cannot bind to its receptor, d) resulting in decrease in uptake of glucose by organs likes muscles. This ultimately results in increased blood glucose levels increases and end in the development of T2DM.
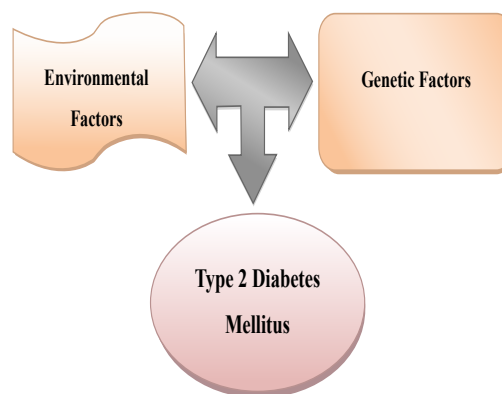

Figure 2: Factors involved in development of T2DM.

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to rare genetic disorders 5-10% patients and remaining 70-85% patients are poorly defined and these 70-85% are the typical T2DM (Type 2 diabetes mellitus) patients as previously reported [1]. It is characterized by defect in insulin secretion by β-cells in pancreatic islets and insulin resistance [2]. It affects health quality and life expectancy of the patients [3]. Type 2 diabetes mellitus is associated with several acute and chronic complications like dehydration, hyperosmotic state leading toward hyperosmolar coma and blood vessel disease respectively.

The escalating rate of Type 2 Diabetes (T2D) has made it the important global health challenge [4]. It has been estimated that 366 million people worldwide suffered from diabetes in 2011 and this number will increase to 552 million till 2030 [5]. Among those people suffering from diabetes 95% have T2D [6]. Prevalence of diabetes is increasing rapidly not only in other countries but in Pakistan also. In Asia diabetes is most prevalent in India which is about 31.7 million. Pakistan is sixth among world in which prevalence of diabetes being 5.2 million in 2000 and estimated to be 13.9 in 2030 [7]. In Pakistan, prevalence of newly diagnosed cases of diabetes is 15.1% in men and 6.8% in women in urban areas while 5.0% in men and 4.8% in women in rural areas [8].

Forms of T2DM

Types of T2DM include maturity-onset diabetes of youth (MODY), latent adult-onset autoimmune diabetes (LADA), secondary to rare genetic disorders and the typical T2DM.

MODY

MODY was first described by Tattersall and Fajan in 1974 for young diabetic patients treated without insulin for two years after diagnosis [9]. It is diagnosed at age less than 25 years [10]. MODY is the old term based on old classification of diabetes. MODY is the monogenic genetic form of T2DM. It is inherited in autosomal dominant mode [11]. It is heterogeneous disorder characterized by impaired beta-cells of pancreas [12]. Till now 7 genes have been reported to be associated with MODY. Frequencies of association of these genes associated with MODY differ in different population with 2 and 3 being predominant over others. Identification of these genes has helped to better understand the molecular and clinical diagnosis of MODY. Other genes associated with MODY X are yet to be identified [13]. MODY is classified into subtypes in relation to genes involved [11] (Table 1).

LADA

Latent autoimmune diabetes in young (LADA) a special subtype of diabetes first characterized in early 1980s by Pittman et al. [14] is often misdiagnosed as T2DM is diagnosed after age 35 years. It is a slow progressive form of adult-onset autoimmune diabetes. It is noninsulin-dependent at the time of clinical diagnosis and presence of circulating glutamic acid decarboxylase-65 (GAD65) autoantibodies and/or islet cell antibodies is the main diagnostic criteria [15,16]. There is problem with classification of LADA as it is between type 1 and type 2 diabetes [17]. So it is usually classified as type 2 diabetes with GAD antibodies due to presence of autoimmunity [15]. It is initially treated with diet control/oral hypoglyceamics without insulin injection use for up to several years after diagnosis [18]. LADA could be considered as admixture of T1DM and T2DM as it shares genetics with both type 1 (HLA, INS VNTR and PTPN22) and type 2 (TCF7L2) diabetes [19].

Diabetes: Other monogenic forms and Secondary to rare genetic disorders

Genes associated with other monogenic forms of T2DM have also been identified and T2DM is also found to be associated with other syndromes and rare genetic disorders that are also monogenic. These genetic disorders include deafness, optic atrophy, Wolfram syndrome, renal and urogenital system structural anomalies, neurological, renal disease, DEND syndrome (developmental delay, epilepsy and neonatal diabetes), partial lipodystrophy, congenital generalized lipodystrophy and skeletal lytic lesions etc [20,21]. The genes associated with these syndromes are shown in table 2.

Heterogeneous multi-factorial T2DM

As described earlier, that 70-85% poorly defined diabetic patients are typical T2DM patients. Because of the heterogeneity of T2DM multiple genes and factors are involved in various combinations [22]. Although environmental factors play an important role in T2D development but genetic factor also influences susceptibility [23]. Genes predisposing to multi-factorial T2DM had been a challenge in the past and despite previous strenuous efforts geneticists were unable to identify genuine susceptibility loci until recent advent of genome-wide association scans (GWAS) has altered the situation and provided better understanding and insight into the T2DM susceptibility genes, increase identification of susceptibility loci and pathogenesis

MODY Sub-Type	Gene Affected	Protein Affected	Locus	Gene Function	Primary Defect
Type 1	HNF4 alpha	Hepatocyte nuclear factor 4 alpha	20q	Transcription factor (Nuclear factor)	Pancreas
Type 2	GCK	Glucokinase	7p15-p13	Hexokinase IV	Pancreas/Liver
Type 3	TCF1	Hepatocyte nuclear factor 1 alpha	12q24.2	Transcription factor (Homeodomain)	Pancreas/Kidney
Type 4	IPF1	insulin promoter factor-1	13q12.1	Transcription factor (Homeodomain)	Pancreas
Type 5	TCF2	Hepatocyte nuclear factor 1 beta	17q12	Transcription factor (Homeodomain)	Kidney/Pancreas
Type 6	Neuro D1	Neurogenic differentiation factor 1	2q	Transcription factor (bHLH)	Pancreas
Type 7	KLF11	Kruppel-like factor 11	2p25	Transforming growth factor-beta inducible-early growth response 2	Pancreas
Type 8	CEL	Bile salt dependent lipase	9q34.3	Hydrolyze cholesterol esters as well as a variety of other dietary esters (OMIM 114840)	Pancreas
Type 9	PAX4	Paired domain gene 4	7q32	Transcription factor (paired domain gene 4)	Pancreas
Type 10	INS	Insulin	11p15.5	Beta cells of the islets of Langerhans	NF-kappa-B
Type 11	BLK	Tyrosine kinase B-Lymphocyte specific	8p23-p22	Tyrosine kinase (B lymphocytes)	MIN6 beta cells

Table 1: Sub-types of MODY.

Gene Affected	Protein Affected	Locus	Gene Function	Primary Defect
WFS1	Wolframin	4p16.1	10 transmembrane domain protein, function unknown	Diabetes insipidus and mellitus with optic atrophy and deafness (DIDMOAD); Wolfram Syndrome
ZCD2	ERIS	4q22-q24	Zinc finger protein ZCD2	Wolfram Syndrome 2
INS	Insulin	11p15.5	Hormone	Mutation in insulin, proinsulin, and proinsulin processing
PTF1A	Pancreas transcription factor 1	10p12	Alpha subunit of PTF1	Permanent neonatal diabetes with cerebellar agenesis
EIF2AK3	PERK	2p12	Pancreatic eIF2-alpha kinase	Wolcott-Rallison Syndrome
Mitochondrial genome	MIDD	Mutation at 3243 mtDNA	tRNA for leucine	Maternally inherited diabetes and deafness; other mitochondrial mutation also observed
Mitochondrial genome		Mutation at 14709 mtDNA	tRNA for glutamic acid	Mitochondrial myopathy with diabetes
KCNJ11	Kir6.2	11p15.1	Potassium channel	Permanent and transient neonatal diabetes
ABCC8	Sur1	11p15.1	Sulfonylurea receptor	Permanent and transient neonatal diabetes
PLAGL1 (ZAC)/ HYMA1	Pleomorhpic adenoma gene 1; hydatidiform mole transcript	11p15.1	Plagl1 - Nuclear zinc finger protein	Imprinted region, exact gene unclear; transient neonatal diabetes type 1
INSR	Insulin receptor	19p13	Receptor tyrosine kinase	Insulin-resistant diabetes with various phenotypes: leprechaunism, Rabson-Mendenhall or type A syndrome
AKT2	PKB-beta	19q1	Serine-threonine kinase	Severe insulin resistance
LMNA	Lamin A/C	1q21	Inner nuclear membrane protein	Face-sparing partial lipodystrophy with peripheral fat loss; mutations also associated with cardiomyopathy; muscular dystrophy; and Hutchinson-Gilford Progeria
LMNB2	Lamin B2	19p13	Inner nuclear membrane protein	Partial lipodystrophy sparing legs (Barraquer-Simons Syndrome)
PPARG	Peroxisome proliferator activated receptor γ	3p25	Nuclear receptor for prostaglands and thiazolidine-diones	Rare variants in ligand binding Domain associated with insulin resistance, hypertension, buttock lipodystrophy
AGPAT2	1-acyl glycerol-3-phosphophate O-acyltransferase 2	9q34	Enzyme of phospholipid metabolism	Congenital generalized lipodystrophy with skeletal lytic lesions (Berardinelli-Seip Syndrome)
BSCL2	Seipin	11q13	398 amino acid protein of unknown function	Congenital generalized lipodystrophy, learning disabilities

Table 2: Genes associated with monogenic diabetes and secondary to rare genetic disorders.

of T2DM [24]. The number of loci showing significant associations with T2DM has increased from 2 identified by older approaches to >70 new established genetic loci by GWAS that efficiently detect multiple small effect common variants. Many of the genes identified so far are involved in encoding proteins necessary for insulin secretion, glucose metabolism and beta-cell function [22,25]. Many of the genes identified so far are involved in encoding proteins necessary for insulin secretion, glucose metabolism and beta-cell function [22]. Many of the susceptibility genes identified so far include PPARG, KCNJ11, TCF7L2, FTO, HHEX/IDE, SLC30A8, CDKAL1, CDKN2A/2B, IGF2BP2, HNF1B, WFS1, JAZF1, CDC123/CAMK1D, TSPAN8/LGR5, THADA, ADAMTS9, NOTCH2, and KCNQ1. But only the first two (PPARG and KCNJ11) have stood the test of time and shown to influence risk of T2DM in multiple studies [26]. But often there is limitation to detect rare variants with stronger effect. Still GWAS is the best method to detect and identify new additional genes in various populations that would provide a more elaborate genetic architecture of disease pathophysiology. More population wise studies will enable us to define function of newly identified loci and genes in pathogenesis of T2D. Common disease-common variant hypothesis is the common strategy used for illustrating inherited components of complex disease. It had been proven true in case of PPARG2 association with T2D and for some other diseases. But mostly identified T2D loci are common variants with small effects [27].

First GWAS for T2D was published by French scientists (Sladek et al.) [28] ho identified association of zinc transporter and member of solute carrier family SLC30A8, HHEX, TCF7L2 and KCNJ11 with T2D [28]. Within same year three other GWAS and deCODE researchers confirmed the association of these genes with T2D [29-32]. A GWAS in Japanese population was shown to be linked to 6 loci (IGF2BP2, CDKN2A/B, KCNJ11, HHEX, SLC30A8, and CDKAL1) previously reported and no novel loci were identified. Also significant association of the SNPs in FTO gene with BMI in the control subjects was reported [33]. Meta-analysis of three T2D GWAS by the Diabetes Genetics Replication And Meta-analysis (DIAGRAM) consortium using 2.2 million SNPs identified additional six novel loci with strong association including CDC123, JAZF1, THADA, ADAMTS9, TSPAN8, and NOTCH2 [34]. Association of FTO gene that was reported for obesity [35] previously was confirmed by this and other replication studies. Association of TCF7L2 gene was replicated with identification of novel regions on chromosome 7, 18p, 2p and 13p by GWAS in African American. The candidate genes in these regions are TCF7L1, VAMP5, VAMP8, CDK8, INSIG2, IPF1, PAX8, IL18R1, members of the IL1 and IL1 receptor families, and MAP4K4 [36]. GWAS showed that diabetes-associated variants in CDKAL1, CDKN2B, HHEX/IDE, IGF2BP2, KCNJ11, SLC30A8 and TCF7L2 account for 2.0-8.5% of variance of T2DM-related traits and have a role in disease aetiology by physiological alterations leading to T2DM, such as glucose intolerance, impaired insulin secretion or insulin resistance. These variants were found to account for 2.0–8.5% of the variance of T2DM-related traits [37].

A large scale association analysis of 8,130 T2D cases and 38,987

controls of European descent identified new twelve T2D loci BCL11A, ZBED3, KLF14, TPS53INP1, CHCHD9, KCNQ1, CENTD2, HMGA2, HNF1A, ZFAND6, PRC1 extending to chromosome X gene DUSP9. These identified loci not only affect insulin action and β cell function but also show evidence of association of genes involved in cell cycle to T2D [38].

The majority of GWAS for T2D have been performed on European population. The GWAS that has been carried out in non-European population especially those with unique cultural and demographic histories and biological traits, like population originating from Indian subcontinent (Pakistan, India and Bangladesh) so far are limited to provide a better insight into the 'genetic landscape of disease' in these populations. GWAS results in other population cannot be used to predict risk in South Asian population. Small number of studies carried out so far not only replicated some previously reported loci but also identified some new susceptibility locus that were not reported to be associated with T2D in other populations. Meta-analysis of European ancestry population including Caucasian identifies new locus KCNQ1 (rs 231362) and HNF1A (overlap between monogenic and multifactorial forms of diabetes). The new KCNQ1 locus was confirmed by a later study carried out in South Asian from India and US [38,39]. Replication of GWA validated variants in Pakistani population of Mirpur, Azad Kashmir region resulted in replication of 13 variants including KCNQ1, JAZF1, IRS1, KLF14, CHCHD9 and DUSP9 that were not previously reported to be associated with T2D in South Asian population [40].

Metanalysis of 39 multiethnic population identifies SREBF1, TH/INS (study-wide significance $p<2.4 \times 10^{-6}$) and GATAD2A/CILP2/PBX4 (genome-wide significance $p=5.7\times10^{-9}$) as additional locus with one that were already known loci suggesting considerable overlap across various ethnic groups [41]. Meta-analysis was carried out including 34,840 cases and 114981 controls of European Descent and Pakistan in order to better understand genetic architecture and pathogenesis of T2D. The study identified ten new unreported T2D loci along with two that showed sex differentiated association (ZMIZ1, ANK1, KLHDC5, TLE1, ANKRD55, CILP2, MC4R, BCAR1 and HMG20A, GRB14, repectively) [42]. A recent GWAS study in Punjabi Sikhs from India identified a novel locus in the SGCG gene (rs9552911) contributing to T2D susceptibility along with six suggestive associations at HMG1L1/CTCFL, PLXNA4, SCAP, and chr5p11 [25]. Recent GWAS in South Asian have reported new variants so large scale meta-analyses and GWA studies that are population specific are needed to improve understanding genetic architecture and pathogenesis of T2D.

Metaanalysis of two Hispanic studies reported association of T2DM with two known genes, HNF1A and KCNQ1 and the unreported C14orf70 [43]. Two novel loci (PTPRD, SRR) and associated with T2DM susceptibility were identified in Han Chinese population in a two-stage GWAS. The study also showed involvement of KCNQ1 that showed susceptibility to T2DM in Japanese, European and Hispanic population [44]. Linkage to chromosome 6q21-q23 and 1q21-q24 was reported in Chinese and Northern European Caucasians in two separate studies [45,46]. In African American families susceptibility was found in genes VAMP5, VAMP8, TCF7L1, IPF1, PAX8, IL18R1, MAP4K4, CDK8 and members of IL1 and IL1R families by genome-wide linkage [36]. IGF2BP, CDKN2A, KCNJ11, HHEX, SLC30A8 and CDKAL1 are associated with T2DM in Japanese population. These genes are strong candidates associated with T2DM susceptibility in various ethnicities as reported in different GWAS [33]. Hepatocyte nuclear factor-4 (HNF4) is a transcription factor that plays an important role in expression of glucose metabolism genes has been associated with T2DM in Ashkenazi Jewish population and Finland families [47,48]. Polymorphisms of TCF7L2 gene associated with T2DM susceptibility has been reported in diverse ethnicities like European, West African, Danish, Icelandic, East Asian, French Dutch, Caucasian, and Brazilian etc [28,49-52]. Variations in other type 2 associated genes like TFAP2B [53], Calpain-10 (first gene to be identified associated with T2DM susceptibility in 1996) [54], KCNJ11 [22], FTO, HHEX, IGF2BP2, SLC30A8 and PPARG discovered in GWAS are also associated with gestational diabetes in women of Korean ancestry [55]. The role of inflammation in pathogenesis of type 2 diabetes was studied by Hu et al. in women and his study showed that Elevated C-reactive proteins were strong predictor of T2DM and arbitrate TNF-R2 and IL-6 association with T2DM [56]. Also significant association of the SNPs in FTO gene with BMI in the control subjects was reported [33]. GWAS showed that diabetes-associated variants in CDKAL1, CDKN2B, HHEX/IDE, IGF2BP2, KCNJ11, SLC30A8 and TCF7L2 account for 2.0-8.5% of variance of T2DM-related traits and have a role in disease etiology by physiological alterations leading to T2DM, such as glucose intolerance, impaired insulin secretion or insulin resistance. These variants were found to account for 2.0–8.5% of the variance of T2DM-related traits [37]. Meta-analysis of European population showed novel association of X-chromosomal locus near DUSP9 and HNF1A that is implicated in both monogenic and polygenic T2DM. These loci control and regulate insulin action and β-cell function. This study also proved the involvement of genes of cell cycle indicating influence of unrelated traits in development of T2DM [37]. These studies will help to better understand involvement of genes like PPARG, KCNJ11, and KCNQ1 etc. in susceptibility to T2DM.

Pharmacogenomics of T2DM

Pharmacogenomics is the field to study the relationship between effects of drug response due to individual's genetic variation. It will help to create personal medicine adapted to one's genetic content.
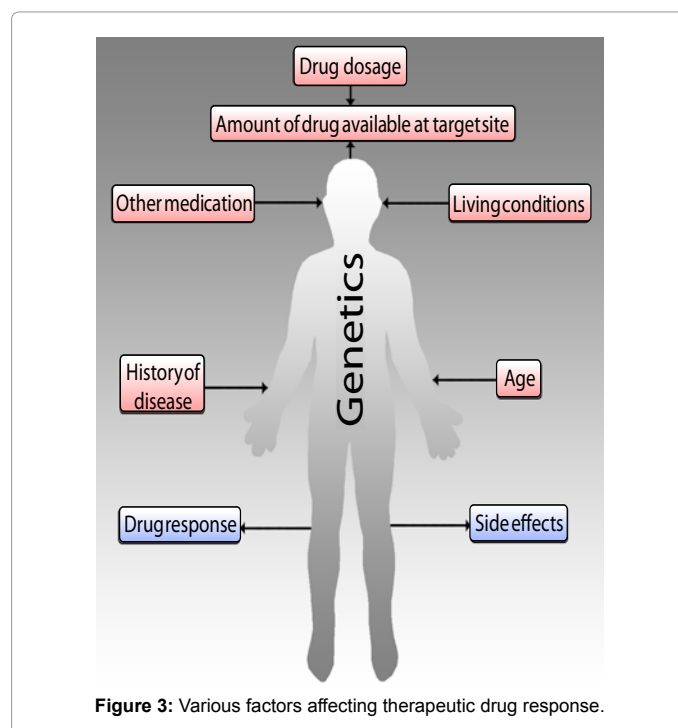

Figure 3: Various factors affecting therapeutic drug response.

Drug	Mechanism of Action	Transporter gene/protein	Response affecting Polymorphism
Sulfonylureas	Increase β-cell insulin secretion by a glucose-independent mechanism	Not studied	CYP2C9 *2/*2, *2/*3, *3/*3, TCF7L2, E23K variant of KCNJ11
Meglitinides	Increase β-cell insulin secretion by a glucose-independent mechanism	SLCO1B1	CYPC8*1/*3, CYP2C9*3
DPP4 inhibitors	Increase insulin secretion by a glucose-dependent mechanism Suppress glucagon secretion by a glucose-dependent mechanism	Incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)	TCF7L2, MTNR1B
GLP1 receptor agonists	Increase insulin secretion by a glucose-dependent mechanism Suppress glucagon secretion by a glucose-dependent mechanism	GLP receptor	T149M polymorphism
Thiazolidinediones	Decrease insulin resistance	SLCO1B1 (OATP1B1)	CYP2C8*3 and *4, PPARG Ala12
Metformin	Decrease insulin resistance	SLC22A1 (OCT1) SLC22A2 (OCT2)	SNP rs622342 in SLC22A1 gene encoding OCT1
α-Glucosidase inhibitors	Act within the gastrointestinal tract to lower postprandial glucose excursions		Pro12Ala of PPARG, Gly482 of PGC1A, TT genotype of APM1 polymorphism +276 G/T

(Partly adapted from Schroner et al. [68] and Holstein et al. [61])

Table 3: Polymorphisms affecting drug response.

Various studies have now elaborated the effect of polymorphisms on drug response. Response to T2DM treatment vary depending on complications, disease duration and whether responder or not so the treatment based on pharmacogenomics will reduce the risk before the symptoms of T2DM appear. Most medications in practice now-a-days for T2DM are not based on specific molecular targets and disease pathogenesis knowledge. Understanding of pathogenic mechanisms has led to discovery of new avenues of drug targets [57,58] (Figure 3).

Nine classes of drugs have been approved for treatment of diabetes with exercise regimens and diet control. These include insulins, sulfonylureas, glinides, biguanides, α-glucosidase inhibitors, thiazolidinediones, glucagon-like peptide 1 mimetics, amylin mimetics, and dipeptidyl peptidase 4 inhibitors [59] but still there is no single medication that can maintain optimal glycemic level. Polymorphisms in TCF7L2, PPARG, cytochrome P450 drug metabolizing enzymes etc modify drug response to metformin, sulphonylureas, DPP4 inhibitors, thiazolidinediones and meglitinides [60]. PPARG and KCJN11 the first variants that were reproducible are the site of action for thiazolidinediones and sulfonylureas, respectively. Variation in TCF7L2 has been found to be associated with change in insulin secretory response to GLP-1 and variation in HbA1C level after the introduction of sulfonylureas. Similarly polymorphism in organic cation transporter-1 (OCT-1) decreased the response to metformin in a study conducted by Shu et al. [61] while another studied conducted by Becker et al. [62] was in contrast to prior study. Many other studies have also been reported but still there is a relative lack of studies in pharmacogenetics of T2DM and in many other diseases [61-66] (Table 3).

However complex factors and genetic heterogeneity makes it difficult to study role of genetic factors in pharmacotherapy and personalized medicines. Advances in GWAS and pharmacogenetics will reveal new genetic variants that modify drug response to diabetes and development of first-line therapy [67,68].

Conclusion

Findings from diverse genetic studies like candidate gene study, linkage analysis, GWAS and animal models will help in identification of disease pathogenesis, regulation and interaction of various factors that influence T2DM. Genetic heterogeneity makes it challenging to develop personalized medicines but GWAS not only will help to better understand the disease but to increase knowledge about complex diseases treatment and management. Genomic studies provided a great insight into pharmacogenetics and resulted in understanding of pharmacotherapy. In future these studies will help in development of personalized medication for T2DM.

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