Review Article

Genetics of Type 2 Diabetes: Insights into the Pathogenesis and Its Clinical Application

Xue Sun,¹ Weihui Yu,² and Cheng Hu^{1,3}

¹ Shanghai Diabetes Institute, Shanghai Clinical Center for Diabetes, Shanghai Key Clinical Center for Metabolic Disease, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai 200233, China

² Department of Endocrinology and Metabolism, Wenzhou Medical University Affiliated First Hospital, Wenzhou 325000, China

³ Shanghai Jiao Tong University Affiliated Sixth People's Hospital, South Branch, Shanghai 200233, China

Correspondence should be addressed to Cheng Hu; alfredhc@sjtu.edu.cn

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With rapidly increasing prevalence, diabetes has become one of the major causes of mortality worldwide. According to the latest studies, genetic information makes substantial contributions towards the prediction of diabetes risk and individualized antidiabetic treatment. To date, approximately 70 susceptibility genes have been identified as being associated with type 2 diabetes (T2D) at a genome-wide significant level ($P < 5 \times 10^{-8}$). However, all the genetic loci identified so far account for only about 10% of the overall heritability of T2D. In addition, how these novel susceptibility loci correlate with the pathophysiology of the disease remains largely unknown. This review covers the major genetic studies on the risk of T2D based on ethnicity and briefly discusses the potential mechanisms and clinical utility of the genetic information underlying T2D.

1. Introduction

The prevalence of type 2 diabetes (T2D) is rising rapidly owing to increased economic growth and lifestyle changes in both developed and developing countries. According to a recent report, the number of diabetics is estimated to reach 439 million by 2030 worldwide [1]. Therefore, strategies to prevent and treat diabetes are urgently needed in order to stem this global pandemic. It is well known that T2D is caused by β -cell dysfunction and/or insulin resistance, which is promoted by multifactorial genetic or environmental factors. Over the years, linkage analysis, candidate gene approach, large-scale association studies, and genome-wide association studies (GWAS) have successfully identified multiple genes that contribute to T2D susceptibility. Combined analyses of these loci, such as construction of genetic risk scores, have contributed significantly to the prediction of T2D diabetes and thus facilitated the adoption of early diagnosis and preventative strategies to reduce this growing disease burden [2–5].

Pharmacogenomics is an emerging discipline that highlights the role of inherited and acquired genetic variations

in drug response and which is beneficial for appropriate selection of antidiabetic drugs [6]. So far, pharmacogenomics has proven to be valuable in guiding therapeutic choices in maturity onset diabetes in the young (MODY) and in neonatal diabetes; however, its extension to T2D still needs detailed studies [7]. The present review summarizes recent genetic research on T2D in both ethnic and chronologic contexts and briefly discusses the potential mechanisms and clinical utilities of genetic information in T2D.

2. Advances in Type 2 Diabetes Genetic Research

Linkage analysis, candidate gene approach, large-scale association studies, and GWAS have identified approximately 70 loci conferring susceptibility to T2D. Among them, 45 loci were identified in European populations (Table 1), and the other 29 loci were identified in Asian populations, especially in East and South Asians (Tables 2 and 3). The immediate benefit derived from these findings was the better understanding of the pathophysiology of T2D.

TABLE 1: European-derived susceptibility loci for type 2 diabetes.

	Locus	SNP	Chr.	Position	Allele (risk/other)	RAF*	OR	Probable mechanism	
2000	<i>PPARγ</i> [8]	rs1801282	3	12368125	C/G	0.92	1.14	Insulin action	Candidate and large-scale association study
2003	<i>KCNJ11</i> [9]	rs5219	11	17366148	T/C	0.5	1.14	β -Cell function	Candidate and large-scale association study
2006	<i>TCF7L2</i> [10]	rs7903146	10	114748339	T/C	0.25	1.37	β -Cell function	Candidate and large-scale association study
2007	<i>WFS1</i> [11]	rs10010131	4	6343816	G/A	0.6	1.11	β -Cell function	Candidate and large-scale association study
2007	<i>HNF1B</i> [12]	rs4430796	17	rs4430796	A/G	0.47	1.1	β -Cell function	Candidate and large-scale association study
2007	<i>IGF2BP2</i> [13–15]	rs4402960	3	186994381	T/G	0.29	1.14	β -Cell function	GWAS
2007	<i>CDKN2A-CDKN2B</i> [13–15]	rs10811661	9	rs10811661	T/C	0.79	1.2	β -Cell function	GWAS
2007	<i>CDKAL1</i> [13–16]	rs10946398	6	20769013	C/A	0.31	1.12	β -Cell function	GWAS
2007	<i>SLC30A8</i> [17]	rs13266634	8	118253964	C/T	0.75	1.12	β -Cell function	GWAS
2007	<i>HHEX/IDE</i> [17]	rs1111875	10	94452862	C/T	0.56	1.13	β -Cell function	GWAS
2007	<i>FTO</i> [13, 15, 18]	rs8050136	16	rs8050136	A/C	0.45	1.17	Obesity	GWAS
2008	<i>NOTCH2</i> [19]	rs10923931	1	120230001	T/G	0.106	1.13	Unknown	GWAS
2008	<i>ADAMTS9</i> [19]	rs4607103	3	64686944	C/T	0.761	1.09	Insulin action	GWAS
2008	<i>THADA</i> [19]	rs7578597	2	43644474	T/C	0.902	1.15	β -Cell function	GWAS
2008	<i>TSPAN8/LGR5</i> [19]	rs7961581	12	69949369	C/T	0.269	1.09	β -Cell function	GWAS
2008	<i>CDC123/CAMK1D</i> [19]	rs12779790	10	12368016	G/A	0.183	1.11	β -Cell function	GWAS
2008	<i>JAZF1</i> [19]	rs864745	7	28147081	T/C	0.501	1.1	β -Cell function	GWAS
2009	<i>MTNR1B</i> [20]	rs1387153	11	92313476	T/C	0.283	1.15	β -Cell function	GWAS
2009	<i>IRS1</i> [21]	rs2943641	2	226801989	C/T	0.633	1.19	Insulin action	GWAS
2010	<i>DGKB/TMEM195</i> [22]	rs2191349	7	15030834	T/G	0.333	1.06	β -Cell function	GWAS
2010	<i>GCKR</i> [22]	rs780094	2	27594741	C/T	0.394	1.06	Insulin action	GWAS
2010	<i>GCK</i> [22]	rs4607517	7	44202193	A/G	0.195	1.07	β -Cell function	GWAS
2010	<i>PROX1</i> [22]	rs340874	1	212225879	C/T	0.492	1.07	β -Cell function	GWAS
2010	<i>ADCY5</i> [22]	rs11708067	3	124548468	A/G	0.226	1.12	β -Cell function	GWAS
2010	<i>RBMS1/ITGB6</i> [23]	rs7593730	2	160879700	C/T	0.23	0.9	Insulin action	GWAS
2010	<i>KCNQ1</i> [24]	rs231362	11	2648047	G/A	0.52	1.08	β -Cell function	GWAS
2010	<i>DUSP9</i> [24]	rs5945326	X	152553116	A/G	0.79	1.27	Insulin action	GWAS
2010	<i>PRCI</i> [24]	rs8042680	15	89322341	A/C	0.22	1.07	Unknown	GWAS
2010	<i>ZFAND6</i> [24]	rs11634397	15	78219277	G/A	0.6	1.06	Unknown	GWAS
2010	<i>HNF1A</i> [24]	rs7957197	12	119945069	T/A	0.85	1.07	Unknown	GWAS
2010	<i>HMGA2</i> [24]	rs1531343	12	64461161	C/G	0.1	1.1	Insulin action	GWAS
2010	<i>CENTD2</i> [24]	rs1552224	11	72110746	A/C	0.88	1.14	β -Cell function	GWAS
2010	<i>CHCHD9</i> [24]	rs13292136	9	81141948	C/T	0.93	1.11	Unknown	GWAS
2010	<i>TP53INP1</i> [24]	rs896854	8	96029687	T/C	0.48	1.06	Unknown	GWAS
2010	<i>KLF14</i> [24]	rs972283	7	130117394	G/A	0.55	1.07	Insulin action	GWAS
2010	<i>ZBED3</i> [24]	rs4457053	5	76460705	G/A	0.26	1.08	Unknown	GWAS
2010	<i>BCL11A</i> [24]	rs243021	2	60438323	A/G	0.46	1.08	Unknown	GWAS

TABLE 1: Continued.

	Locus	SNP	Chr.	Position	Allele (risk/other)	RAF*	OR	Probable mechanism	
2012	<i>HMG20A</i> [25]	rs7177055	15	75,619,817	A/G	0.68	1.08	Unknown	GWAS
2012	<i>GRB14</i> [25]	rs13389219	2	165,237,122	C/T	0.6	1.07	Insulin action	GWAS
2012	<i>ZMIZ1</i> [25]	rs12571751	10	80,612,637	A/G	0.52	1.08	Unknown	GWAS
2012	<i>ANK1</i> [25]	rs516946	8	41,638,405	C/T	0.76	1.09	β -cell function	GWAS
2012	<i>KLHDC5</i> [25]	rs10842994	12	27,856,417	C/T	0.8	1.1	Unknown	GWAS
2012	<i>TLE1</i> [25]	rs2796441	9	83,498,768	G/A	0.57	1.07	Unknown	GWAS
2012	<i>ANKRD55</i> [25]	rs459193	5	55,842,508	G/A	0.7	1.08	Insulin action	GWAS
2012	<i>CILP2</i> [25]	rs10401969	19	19,268,718	C/T	0.08	1.13	Unknown	GWAS
2012	<i>MC4R</i> [25]	rs12970134	18	56,035,730	A/G	0.27	1.08	Unknown	GWAS
2012	<i>BCAR1</i> [25]	rs7202877	16	73,804,746	T/G	0.89	1.12	β -Cell function	GWAS

* Data were derived from HapMap East Asian or original studies. Position is given for NCBI Build 36.
SNP: single nucleotide polymorphism; Chr.: chromosome; RAF: risk allele frequency; OR: odds ratio.

TABLE 2: Type 2 diabetes susceptibility loci identified in East Asians.

	Locus	SNP	Chr.	Position	Allele (risk/other)	RAF*	OR	Probable mechanism	
2009	<i>KCNQ1</i> [26]	rs2237892	11	2796327	C/T	0.683	1.43	β -Cell function	GWAS
2010	<i>UBE2E2</i> [27]	rs7612463	3	23311454	A/C	0.134	1.19	Unknown	GWAS
2010	<i>C2CD4A-C2CD4B</i> [27]	rs7172432	15	60183681	A/G	0.42	1.13	Unknown	GWAS
2010	<i>SPRY2</i> [28]	rs1359790	13	79615157	G/A	0.273	1.15	Unknown	GWAS
2010	<i>CDC123/CAM KID</i> [28]	rs10906115	10	12355003	A/G	0.561	1.13	Unknown	GWAS
2010	<i>SRR</i> [29]	rs391300	17	2163008	G/A	0.367	1.28	β -Cell function	GWAS
2010	<i>PTPRD</i> [29]	rs17584499	9	8869118	T/C	0.226	1.57	Insulin action	GWAS
2011	<i>MAEA</i> [30]	rs6815464	4	1299901	C/G	0.640	1.13	Unknown	GWAS
2011	<i>PSMD6</i> [30]	rs831571	3	64023337	C/T	0.688	1.09	Unknown	GWAS
2011	<i>ZFAND3</i> [30]	rs9470794	6	38214822	C/T	0.203	1.12	Unknown	GWAS
2011	<i>GCCI-PAX4</i> [30]	rs6467136	7	126952194	G/A	0.182	1.11	Unknown	GWAS
2011	<i>KCNK16</i> [30]	rs1535500	6	39392028	T/G	0.398	1.08	β -Cell function	GWAS
2011	<i>PEPD</i> [30]	rs3786897	19	38584848	A/G	0.547	1.1	Unknown	GWAS
2011	<i>FITM2-R3HD</i> [30]	rs6017317	20	42380380	G/T	0.545	1.09	β -Cell function	GWAS
2011	<i>GLIS3</i> [30]	rs7041847	9	4277466	A/G	0.529	1.1	β -Cell function	GWAS
2012	<i>ANK1</i> [31]	rs515071	8	41,638,405	C/T	0.8	1.18	Unknown	GWAS
2013	<i>GRK5</i> [32]	rs10886471	10	121139393	C/T	0.756	1.12	Insulin action	GWAS
2013	<i>RASGRP1</i> [32]	rs7403531	15	36610197	T/C	0.317	1.1	β -Cell function	GWAS
2013	<i>PAX4</i> [33]	rs10229583	7	127034139	G/A	0.829	1.18	Unknown	GWAS
2013	<i>MIR129-LEP</i> [34]	rs791595	7	127650038	A/G	0.08	1.17	Unknown	GWAS
2013	<i>SLC16A13</i> [34]	rs312457	17	6881117	G/A	0.078	1.2	Unknown	GWAS
2013	<i>GPSM1</i> [34]	rs11787792	9	138371969	A/G	0.874	1.15	Unknown	GWAS

* Data were derived from HapMap East Asian or original studies. Position is given for NCBI Build 36.
SNP: single nucleotide polymorphism; Chr.: chromosome; RAF: risk allele frequency; OR: odds ratio.

2.1. Genetics of Type 2 Diabetes in European Populations

2.1.1. Linkage Analysis, Candidate Gene Approach, and Large-Scale Association Studies. Linkage analysis has proved to be valuable in the exploration of genetic factors of monogenic diseases, such as MODY, neonatal mitochondrial diabetes,

insulin resistance, and Wolfram syndromes [38–40]. However, it has not been particularly useful in identifying the genetic factors for common forms of T2D. Over the years, linkage studies have reported many predisposing associations with chromosomal regions for T2D, including segments in chromosomes 5 and 10, and have identified putative, causative

TABLE 3: Type 2 diabetes susceptibility loci identified in South Asians.

	Locus	SNP	Chr.	Position	Allele (risk/other)	RAF*	OR	Probable mechanism	
2011	<i>ST6GAL1</i> [35]	rs16861329	3	188149155	G/A	0.86	1.09	β -Cell function	GWAS
2011	<i>HNF4A</i> [35]	rs4812829	20	42422681	A/G	0.29	1.09	β -Cell function	GWAS
2011	<i>VPS26A</i> [35]	rs1802295	10	70601480	A/G	0.26	1.08	Unknown	GWAS
2011	<i>AP3S2</i> [35]	rs2028299	15	88175261	C/A	0.31	1.1	Unknown	GWAS
2011	<i>HMG20A</i> [35]	rs7178572	15	75534245	G/A	0.52	1.09	Unknown	GWAS
2011	<i>GRB14</i> [35]	rs3923113	2	165210095	A/C	0.74	1.09	Insulin action	GWAS
2013	<i>TMEM163</i> [36]	rs998451	2	135145758	G/A	1	1.56	β -Cell function	GWAS
2013	<i>SGCG</i> [37]	rs9552911	13	22762657	A/G	0.07	0.67	Unknown	GWAS

* Data were derived from HapMap East Asian or original studies. Position is given for NCBI Build 36.

SNP: single nucleotide polymorphism; Chr.: chromosome; RAF: risk allele frequency; OR: odds ratio.

genetic variants in *CAPN10* [41], *ENPP1* [42], *HNF4A* [43, 44], and *ACDC* (also called *ADIPOQ*) [45], but most of the findings from these reports could not be replicated.

During the past several decades, only a few loci conferring risk of T2D were identified through candidate gene approach with *PPAR γ* Pro12Ala polymorphism being the first reported locus [8]. *PPAR γ* is a transcription factor that plays a pivotal role in adipocyte differentiation. It was reported that *PPAR γ* Pro12Ala variant was associated with increased insulin sensitivity in the general population and thus may protect an individual from T2D [46]. The *KCNJ11* (potassium inwardly rectifying channel subfamily J, member 11) encodes potassium inwardly rectifier 6.2 subunit (Kir6.2) of the ATP-sensitive potassium (K_{ATP}) channel, which has an impact on glucose-dependent insulin secretion in pancreatic β -cells [9]. The E23K variant in this gene demonstrated a robust association with T2D using the candidate gene approach [9]. *WFS1* and *HNF1B* were also uncovered as established genes associated with T2D [11, 12]. *WFS1* encodes wolframin, a membrane glycoprotein that maintains calcium homeostasis of the endoplasmic reticulum. Rare mutations in *WFS1* cause Wolfram syndrome, which is characterized by a significant β -cell loss as a result of enhanced endoplasmic reticulum stress [47–49]. *HNF1B* encodes hepatocyte nuclear factor 1 homeobox B, which is a liver-specific factor of the homeobox-containing basic helix-turn-helix family. Mutation of this gene was demonstrated to cause MODY5 [38].

In 2006, a large-scale association study identified *TCF7L2* as an important genetic factor for T2D in Icelandic individuals [10]. This discovery was a significant breakthrough as this association was then widely confirmed in populations of European origin and other ethnic groups, such as Japanese and American individuals [50–57]. Therefore, *TCF7L2* was regarded as the most significant T2D susceptibility gene identified to date.

2.1.2. Genome-Wide Association Study (GWAS). With the advent of GWAS, exploration of the genetic basis for T2D susceptibility has made significant breakthroughs. In 2007, the results of five genome-wide association studies were published. These studies increased the number of confirmed T2D susceptibility loci to nine (*PPAR γ* , *KCNJ11*, *TCF7L2*,

CDKAL1, *CDKN2A/B*, *IGF2BP2*, *HHEX/IDE*, *FTO*, and *SLC30A8*) [13–18]. Except for *PPAR γ* and *FTO*, which mainly affect insulin sensitivity, all the other genes may affect β -cell function, although the exact mechanisms remain largely unknown [16]. *HHEX*, which is located on chromosome 10q, is a member of the homeobox family and encodes a transcription factor that maybe involved in Wnt signaling [58]. Nevertheless, these studies established the utility of GWAS approach in elucidating complex genetic traits.

In 2008, to increase the power of identifying variants with modest effects, a meta-analysis of three GWAS, including Diabetes Genetics Initiative (DGI), Finland-United States Investigation of NIDDM Genetics (FUSION), and Wellcome Trust Case Control Consortium (WTCCC), were conducted. This study detected at least six previously unknown loci that reached genome-wide significance for association with T2D ($P < 5 \times 10^{-8}$), with the loci being *JAZF1*, *CDC123-CAMK1D*, *TSPAN8-LGR5*, *THADA*, *ADAMTS9*, and *NOTCH2* [19]. Genetic variants in *JAZF1*, *CDC123-CAMK1D*, *TSPAN8-LGR5*, and *THADA* have been reported to affect pancreatic β -cell functions [59, 60].

In 2009, a novel genetic variant rs2943641, which is located adjacent to the insulin receptor substrate 1 gene (*IRS1*), was shown to have a significant association with insulin resistance and hyperinsulinemia and further studies also showed that this variant is implicated in reduced basal *IRS1* protein level and decreased *IRS1*-associated phosphatidylinositol-3-OH kinase activity in human skeletal muscle biopsies [21]. In the same year, a variant near *MTNR1B* was found to be associated with increased fasting plasma glucose level and higher risk of T2D (odds ratio = 1.15, 95% CI = 1.08–1.22, $P = 6.3 \times 10^{-5}$) [20]. Ten GWAS involving a total of 36,610 individuals of European descent and a meta-analysis of 13 case-control studies replicated this result and found that risk alleles in this gene are associated with reduced β -cell function as measured by homeostasis model assessment ($HOMA-\beta$, $P = 1.1 \times 10^{-15}$) [61].

In 2010, a meta-analysis of 21 genome-wide association studies performed by Dupuis and colleagues identified *ADCY5*, *PROX1*, *GCK*, *GCKR*, and *DGKB/TMEM195* as new genetic loci for T2D susceptibility [22]. Among these loci, *DGKB/TMEM195*, *GCK*, *PROX1*, and *ADCY5* mainly affect

β -cell functions, whereas the locus mapped in *GCKR* shows a primary effect on insulin action [22]. In the same year, another genome-wide association study by Qi and colleagues discovered new variants near *RBMS1* and *ITGB6* genes at 2q24, and these variants were found to affect glucose metabolism and insulin resistance [23]. In addition, an expanded meta-analysis of existing GWAS by Voight and colleagues identified 12 new signals with a combined $P < 5 \times 10^{-8}$, including *BCL11A*, *ZBED3*, *KLF14*, *TP53INP1*, *TLE4*, *CENTD2*, *HMGA2*, *HNFI1A*, *PRCI*, *ZFAND6*, *DUSP9*, and *KCNQ1* [24]. *HNFI1A* was previously recognized as the causal gene of MODY3 [62] and also harbored the common variant (G319S) that contributes to early-onset T2D [63, 64]. *DUSP9*, mapped on chromosome X, encodes a member of the family of mitogen-activated protein kinase phosphatase 4, MKP4, which is important in cell cycle regulation and plays pivotal roles in regulating insulin action [65–67].

In 2012, a meta-analysis conducted by Morris and colleagues identified additional ten previously unreported T2D susceptible loci, including *BCAR1*, *MC4R*, *CILP2*, *ANKRD55*, *TLE1*, *KLHDC5*, *MGC21675*, *ANK1*, *ZMIZ1*, and *GRB14* [25]. To assess the potential function of these loci, OGTT was employed to test insulin release and insulin sensitivity. *ANK1* was found to be associated with insulinogenic and disposition indices, indicating that this gene probably had an effect on insulin secretion [68]. In this study, *GRB14* and *ANKRD55* were associated with decreased Matsuda index, an index of insulin sensitivity [68].

As described above, genetic studies of T2D in European populations have made significant progress in our understanding of T2D susceptibility. However, existing data can only provide partial explanation for the heritability of T2D. It is well known that discrepancies exist in allelic frequencies and effect sizes in different ethnic groups. It is, therefore, important to understand whether these variants are also applicable to other ethnic populations.

2.2. Genetics of T2D in East Asians. Epidemiological studies have documented consistent increases in the prevalence of diabetes in Asia, especially in China, with diabetes prevalence having increased from 2.6% in 2000 to 9.7% in 2010 [69]. However, our understanding of the genetic basis of T2D in East Asia remains limited. It is therefore imperative to identify specific genes associated with this disease in East Asians.

In 2008, two papers provided the first reports of GWAS for T2D in East Asian populations and ascertained *KCNQ1* as a new susceptibility locus [70, 71]. *KCNQ1* encodes the pore-forming α -subunit of the voltage-gated K^+ channel (KvLQT1), which is expressed mainly in the heart and pancreas. Its association with T2D was further replicated in Korean [72], Chinese [26], and Singaporean [73] populations, as well as individuals of European descent [70]. Therefore, *KCNQ1* is regarded as the most significant locus for T2D in East Asians. This genetic variant is implicated in insulin secretion, which may be the explanation for its association with T2D [73, 74].

In 2010, another GWAS conducted in a Japanese group identified two new loci in *UBE2E2* and *C2CD4A-C2CD4B*. Genetic variants in *C2CD4A-C2CD4B* were then validated in European populations [27]. When the GWAS reports sprung up in East Asians, Chinese investigators performed their first GWAS in the Han Chinese residing in Taiwan and identified two new susceptible loci for T2D in *PTPRD* (protein tyrosine phosphatase receptor type D) and *SRR* (serine racemase) [29]. *PTPRD* is a protein tyrosine phosphatase and may play a role in the pathogenesis of T2D through increased insulin resistance [75]. *SRR* encodes a serine racemase that synthesizes D-serine from L-serine and which confers risk for T2D via the glutamate signaling pathway [76, 77]. In the same year, a fast-track, multiple-stage study conducted in Han Chinese population by Shu and colleagues discovered a novel genetic susceptibility locus rs1359790, at *13q31.1* for T2D, and this variant was also validated in European Americans, Koreans, and Singapore Chinese [28].

In 2011, in order to identify additional genes in East Asians, Cho and colleagues carried out a meta-analysis of three-stage GWAS in populations of East Asian descent. Compelling evidence for association with T2D of eight novel loci was demonstrated by this study. All of these loci are mapped in or near *GLIS3*, *PEPD*, *FITM2-R3HDM1-HNF4A*, *KCNK16*, *MAEA*, *GCCI-PAX4*, *PSMD6*, and *ZFAND* [30].

In 2012, another GWAS in Japanese populations revealed that rs515071 in *ANK1* was associated with T2D at the genome-wide significance level [31]. *ANK1*, which encodes a member of the ankyrin family, is also reported to be associated with impaired insulin secretion and abnormal level of HbA_{1c} [68, 78]. In addition, GWAS in Beijing and Shanghai populations added two new loci to the list, *GRK5* and *RASGRP1*, and the association signal for *GRK5* seems to be specific to East Asians [32]. *GRK5* is regarded as a positive regulator of insulin sensitivity and this protein is a potential therapeutic target for the treatment of insulin resistance [79].

In 2013, a novel variant rs10229583 at 7q32 near *PAX4* was identified in a meta-analysis of three GWAS from Southern Han Chinese descents [33]. As a member of the paired box family of transcription factors, *PAX4* plays a critical role in pancreatic β -cell development and β -cell functions [80]. Further three new predisposing loci, *MIR129-LEP*, *GPSM1*, and *SLC16A13*, with genome-wide significance for T2D were identified [34]. Rs791595 is located between *MIR129-1* and *LEP*. The coding product of *LEP*, leptin, is closely related to body weight regulation and its deficiency in mice and human causes morbid obesity and diabetes, while the role of *MIR129* in diabetes remains unknown [81].

Besides these newly identified loci, some susceptible genes identified in Caucasians were also replicated in East Asians, such as *PPAR γ* , *KCNJ11*, *TCF2*, *TCF7L2*, *CDKAL1*, *CDKN2A-CDKN2B*, *IDE-KIF11-HHEX*, *IGF2BP2*, *MTNR1B*, *SLC30A8*, *KCNQ1*, *CDC123*, *GLIS3*, *HNFI1B*, and *DUSP9* [32, 82–93].

Together, all these T2D risk loci, initially identified or replicated in East Asians, provide new perspectives on the etiology of T2D and uncover the need for further studies to explore additional loci with strong effects on T2D.

2.3. Genetics of T2D in South Asians. South Asia, with more than a quarter of the world's population, harbors the highest number of patients suffering from T2D [94]. Currently, the number of diabetic patients is reaching 62.4 million, and the number of prediabetic individuals is reaching 77.2 million [95]. Compared to European populations, South Asians are at a fourfold higher risk of T2D [96, 97]. Therefore, significant efforts should be made to identify common genetic variants underlying the T2D risk in individuals of South Asian ancestry.

In 2011, a GWAS in South Asians identified six novel loci harboring disease-predisposing variants, including *GRB14*, *ST6GAL1*, *VPS26A*, *HMG20A*, *AP3S2*, and *HNF4A*. Single nucleotide polymorphisms (SNPs) at *GRB14* were associated with insulin sensitivity and SNPs at *ST6GAL1* and *HNF4A* were associated with pancreatic β -cell function [35].

In 2013, a GWAS performed in Indians identified *TMEM163* on chromosome 2q21 as a new signal for T2D. *TMEM163* encodes a putative vesicular transporter in nerve terminals and shows a plausible effect on T2D by impairing insulin secretion [36]. Concurrently, a novel locus at 13q12 in the *SGCG* gene was identified to confer T2D susceptibility in Punjabi Sikhs from Northern India. This association demonstrated excellent consistency across the three Sikh samples, but no significant association was observed in a large East Asian replication study, indicating that the detected locus is specific to the Indian Punjabi Sikh population [37].

In consideration of India's complex demographic history, cultural diversity, differences in risk allele frequency, and pattern of linkage disequilibrium existing between European and South Asian populations, large replication studies were conducted to evaluate the contribution of European-derived loci in South Asian populations. SNPs in or near *PPARG*, *KCNJ11*, *TCF7L2*, *SLC30A8*, *HHEX*, *CDKN2A/B*, *IGF2BP2*, *CDKAL1*, *FTO*, *KCNQ1*, *JAZF1*, *IRS1*, *KLF14*, *CHCHD9*, and *DUSP9* displayed significant associations with T2D in Pakistani populations, with similar effect sizes as those seen in European populations [98–102].

2.4. Genetics of Type 2 Diabetes in Other Populations. The discovery of new susceptibility loci for T2D by GWAS in different ethnic groups emphasizes the need to conduct more GWAS based on ethnic background. In addition to European and Asian populations, researchers also conducted studies in Pima Indians and Mexican Americans aimed at identifying new risk loci.

In Pima Indians, a few genes have been reported to confer risk of T2D. In 2007, researchers found that variants within *ARHGEF11* nominally increased the risk of T2D, possibly as a result of increased insulin resistance [103]. In 2008, variation within *PCLO* was confirmed to have a modest effect on early-onset T2D, possibly by reduction of insulin action [104]. In 2010, *ACAD10* variation was found to increase T2D risk by impairing insulin sensitivity via abnormal lipid oxidation [105]. Soon afterwards, an *ASK1* variant was identified to confer susceptibility to T2D by decreasing insulin sensitivity owing to reduced *ASK1* expression in skeletal muscle [106]. However, a replication study, which genotyped SNPs mapped

in *CDKAL1*, *SLC30A8*, *HHEX*, *EXT2*, *IGF2BP2*, *LOC387761*, and *FTO* previously associated with T2D in Caucasians, did not provide any evidence for association with T2D or obesity among full-heritage Pima Indians. Instead, they found that *CDKAL1*, *HHEX*, and *EXT2* were evidently associated with either insulin secretion or insulin action in Pima Indians with normal glucose tolerance [107].

Similarly, analysis of T2D risk genes in Mexican American populations had identified several novel candidate loci for T2D, such as rs979752 and rs10500641 near *UBQLNL* and *OR52H1* on chromosome 11, rs2773080 and rs3922812 in or near *RALGPS2* on chromosome 1, and rs1509957 near *EGR2* on chromosome 10 [108]. In 2011, the largest GWAS and meta-analysis of T2D in Mexican populations identified 49 SNPs in eight gene regions (*PER3*, *PARD3B*, *EPHA4*, *TOMM7*, *PTPRD*, *HNT*, *LOC729993*, and *IL34*) and six intergenic regions with an unadjusted *P* value $< 1 \times 10^{-5}$ [109]. In consideration of the fact that all the above loci did not reach genome-wide significance ($P < 5 \times 10^{-8}$), Williams and colleagues analyzed 9.2 million SNPs in 8,214 Mexicans and other Latin Americans and identified a novel locus associated with T2D spanning the solute carriers *SLC16A11* ($P = 3.9 \times 10^{-13}$; odds ratio (OR) = 1.29). They observed that *SLC16A11* mainly localizes with the endoplasmic reticulum membrane protein, calnexin, in liver, salivary gland, and thyroid. Importantly, overexpression of *SLC16A11* in HeLa cells resulted in substantial increases in triacylglycerol, suggesting that *SLC16A11* may have a role in hepatic lipid metabolism [16, 110]. Nevertheless, the role of all these risk loci in the pathogenesis of diabetes remains unclear and needs further investigations.

3. Correlation of the Susceptibility Loci with the Pathogenesis of T2D

With the large number of aforementioned genetic loci susceptible to T2D, the question pertains to how they participate in the pathogenesis of T2D. A great number of studies have suggested that genetic variants in or near *KCNJ11*, *TCF7L2*, *WFS1*, *HNF1B*, *IGF2BP2*, *CDKN2A-CDKN2B*, *CDKAL1*, *SLC30A8*, *HHEX/IDE*, *KCNQ1*, *THADA*, *TSPAN8/LGR5*, *CDC123/CAMK1D*, *JAZF1*, *MTNR1B*, *DGKB/TMEM195*, *GCK*, *PROX1*, *ADCY5*, *SRR*, *CENTD2*, *ST6GAL1*, *HNF4A*, *KCNK16*, *FITM2-R3HDM1-HNF4A*, *GLIS3*, *GRB14*, *ANK1*, *BCAR1*, *RASGRP1*, and *TMEM163* may confer T2D risk through impaired β -cell function [16, 24, 44, 68, 111–114], whereas *PPARG*, *ADAMTS9*, *IRS1*, *GCKR*, *RBMS1/ITGB6*, *PTPRD*, *DUSP9*, *HMGA2*, *KLF14*, *GRB14*, *ANKRD55*, and *GRK5* have an impact on insulin action [21, 24, 115, 116] (Tables 1, 2, and 3). *FTO* and *MC4R*, previously identified genes associated with obesity, appear to confer T2D risk through their primary effects on BMI, but recent GWAS have shown that their effects on T2D were independent of BMI, though *FTO* may have a small but detectable influence on T2D risk through insulin action [117, 118].

3.1. Impact of TCF7L2 on the Risk of T2D. *TCF7L2* is the most intensively studied locus for T2D risk so far. The risk

alleles of *TCF7L2* were associated with enhanced expression of this gene in human islets as well as impaired insulin secretion both *in vitro* and *in vivo*. The authors also observed an impaired incretin effect in subjects carrying risk alleles of *TCF7L2* and proposed the engagement of the enteroinsular axis in T2D [119]. Dennis and colleagues then verified this result and indicated that *TCF7L2* variant rs7903146 affected risk of T2D, at least in part, through modifying the effect of incretins on insulin secretion. This was not due to reduced secretion of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), which exhibit an important physiological role in boosting insulin secretion following meals, but rather due to the effect of *TCF7L2* on the sensitivity of β -cells to incretins [120]. *TCF7L2* has also been linked to altered pancreatic islet morphology as exemplified by increased individual islet size and altered alpha and beta cell ratio/distribution within human islets [121]. This phenomenon is also observed in other *in vivo* or *in vitro* studies [122–124]. This further strengthened the evidence for the role of *TCF7L2*-associated alteration of cell types in islets in the pathogenesis of T2D.

TCF7L2 encodes the transcription factor TCF4 which is related to Wnt signaling pathway and which plays a critical role in the pathogenesis of T2D. The major effector of the canonical Wnt signaling pathway is known as β -catenin/TCF. This bipartite transcription factor is formed by free β -catenin (β -cat) and a member of the TCF protein family, including *TCF7L2* (previously known as TCF-4) [125]. GWAS have revealed the involvement of a Wnt ligand (Wnt-5b), Wnt coreceptor (LRP-5), and the Wnt pathway effector *TCF7L2* in the development of diabetes [126]. Several previous studies also provide evidence that the β -catenin/TCF axis participates in pancreatic cell proliferation and differentiation [127–131]. Treatment of β -cells with purified Wnt protein or activated β -catenin augmented the proliferation of these cells [132]. Intriguingly, deletion of β -catenin within the pancreatic epithelium resulted in an almost complete lack of acinar cells, whereas deletion of β -catenin specifically in differentiated acinar cells had no such effect [128], suggesting that the *TCF7L2*-related Wnt signaling mainly perturbs pancreatic growth but not pancreatic function. However, deletion of islet *TCF7L2* expression from β -cells did not show any demonstrable effects on glucose-stimulated insulin secretion (GSIS) in adult mice, whereas manipulating *TCF7L2* levels in the liver caused hypoglycemia and reduced hepatic glucose production [133]. In concordance with these results, risk alleles in *TCF7L2* were associated with hepatic but not peripheral insulin resistance and enhanced rate of hepatic glucose production in human [119]. Therefore, *TCF7L2*-related disruption of β -cell function is probably the indirect consequence of primary events in liver or other organs/systems.

3.2. Impact of *SCL30A8* on the Risk of T2D. Besides *TCF7L2*, solute carrier family 30 member 8 gene (*SCL30A8*) has also been explored in depth. *SCL30A8* encodes the islet-specific zinc transporter ZnT-8, which delivers zinc ions from cytoplasm into intracellular insulin-containing granules, and

is implicated in insulin maturation and/or storage processes in β -cells [134]. Expression level of ZnT-8 was remarkably downregulated in the pancreas of db/db and Akita mice in the early stage of diabetes [135]. Global *SCL30A8* knockout mice demonstrated reduced plasma insulin, impaired GSIS, and markedly reduced islet zinc content [136]. Remarkably, both ZnT-8 knockout mice and human individuals carrying risk alleles of *SCL30A8* exhibited increased hepatic insulin clearance, with significantly increased c-peptide/insulin ratios [137]. Contrary to the previous findings, overexpression of ZnT-8 in INS-1 cells stimulated zinc accumulation and enhanced GSIS of these cells [138]. Importantly, a recent study discovered that *SCL30A8* gene transcription was regulated by Pdx-1, a β -cell-enriched transcription factor, and involved in the development of islets, through an intrinsic enhancer. Restriction of Pdx-1 in pancreatic islet β -cells correlated with the induction of *SCL30A8* gene and ZnT-8 protein expression [139]. Therefore, the specific pathways by which *SCL30A8* correlates with the pathogenesis of T2D still need further exploration.

It should be noted that a great number of low frequency variants might not be identified by GWAS owing to the required genome-wide significance level. According to the existing studies, many important loci are also obscured as a result of borderline associations. The known variants account for only a small amount of the overall estimated genetic heritability; therefore, there is still a long way to go in terms of understanding the pathogenesis of type 2 diabetes.

4. Clinical Utility of Genetic Information: Prediction of Type 2 Diabetes

One of most important clinical utilities of genetic information is to predict the risk of developing T2D among nondiabetic individuals. This will facilitate the early interventional strategies to prevent or delay the onset of the disease. A vast number of recent studies have constructed genetic risk score models by summing up numerous independently inherited susceptible variants for T2D to evaluate the predictive ability from the current genetic information. For example, the area under the receiver operating characteristic (ROC) curves (AUCs) is used to assess discriminative accuracy of this approach. The AUC value can range from 0.5 to 1.0, where the AUC of 0.5 stands for the lack of discrimination and AUC of 1 stands for perfect discrimination. An AUC value of greater than 0.75 is considered to be clinically useful [140]. Imamura and colleagues created a genetic risk score model using 49 susceptibility alleles (GRS-49) for T2D in a Japanese population and discovered an increased level of AUC with combined GRS-49 and clinical factors (including age, sex, and BMI) compared with each individually. But the AUC value is only 0.773, which shows a clinically modest but statistically significant effect on T2D [141]. This phenomenon is also observed in many other studies from different ethnic groups [142, 143]. Controversially, it was proposed that phenotype-based risk models are superior to models based on 20 common independently inherited diabetes risk alleles in discrimination for T2D, with the observation of only

minimal improvement in accuracy of risk estimation when adding genotypes to phenotype-based risk models [144]. The discrepancy may result from the fact that prediction for T2D using genetic information is largely affected by age. For example, the Framingham Offspring Study conducted with 3,471 subjects followed over 34 years found out that common genetic variations appropriately reclassified younger people for T2D risk beyond clinical risk factors, but it failed in older people [145]. In addition, along with the rapid economic growth and lifestyle changes, we may underscore the role of environmental factors in the pathogenesis of T2D. A recent study suggested that the potential deleterious effect of several T2D loci may be abolished or at least attenuated by higher physical activity levels or healthy lifestyle, whereas they may be augmented by low physical activity and dietary factors that are similar to a Western dietary pattern [146]. Therefore, these inconsistencies will need further investigations.

5. Pharmacogenomics of Type 2 Diabetes

With the advent of GWAS, studies on the roles of inherited and acquired genetic variations in drug response have undergone an evolution from pharmacogenetics into pharmacogenomics, with a shift from the focus on individual candidate genes to GWAS [147]. Clinically, it is often observed that even patients who receive similar antidiabetic regimens demonstrate large variability in drug disposition, glycemic response, tolerability, and incidence of adverse effects [148]. This interindividual variability can be attributed to specific gene polymorphisms involved in the metabolism, transportation, and therapeutic mechanisms of oral antidiabetic drugs. Pharmacogenomics is on the agenda to explore feasible genetic testing to predict treatment outcome, so that appropriate steps could be taken to treat type 2 diabetes more efficiently.

In general, the oral antidiabetic drug (OAD) is the first line treatment for T2D after failure of lifestyle intervention. The most commonly prescribed OADs include sulfonylureas (SU), biguanides, thiazolidinediones (TZDs), glinides, and α -glucosidase inhibitors. To date, numerous pharmacogenetic studies comparing these drugs have been conducted in populations with different ethnic backgrounds. With respect to sulfonylureas, genetic variants at multiple loci such as *KCNJ11*, *ABCC8*, *IRIS1*, *TCF7L2*, *NOS1AP*, *KCNQ1*, *CDKALI*, and *CAPN10* affect pharmacokinetics and/or pharmacodynamics of these drugs [149–157]. Among them, *KCNJ11* encodes a major subunit of the ATP-sensitive K^+ channel, and *ABCC8* encodes a modulator of ATP-sensitive potassium channels (SUR1). They both play pivotal roles in insulin secretion and are both shown in pharmacogenomic studies to impact sulfonylureas efficacy [151, 158]. The Arg (972) IRS-1 variant is associated with increased risk for secondary failure to sulfonylurea and it is noteworthy that the genotype frequency of this variant is twice as high in patients with secondary failure to sulfonylurea compared to the diabetic patients whose blood glucose levels were well controlled with oral therapy [157]. In diabetic patients carrying risk alleles in *NOS1AP* gene, glibenclamide is less effective in

reducing glucose levels. The increased mortality in users of sulfonylurea was also shown in this paper, reminding us of the fact that genetic variation could alter responses to T2D therapy [155]. Consistent with this notion, studies have shown that genetic variants in *SLC22A1*, *SLC22A2*, *SLC47A1*, *SLC47A2*, and *ATM* [159–167] were found to affect metformin efficacy. *SLC22A1* encodes organic cation transporter 1 (OCT1), which participates in the transportation of metformin into hepatocytes. *SLC47A1* encodes the multidrug and toxin extrusion 1 protein (MATE1), which facilitates metformin excretion from hepatocytes into bile. *ATM*, a gene known to be involved in DNA repair and cell cycle control, plays a role in metformin efficacy upstream of AMPK, and variation in this gene alters glycemic responses to metformin [167].

Gene polymorphisms associated with glinide (repaglinide and nateglinide) responses were mapped in *CYP2C8*, *SLCO1B1*, *TCF7L2*, *CYP3A4*, *IGF2BP2*, *SLC30A8*, *KCNQ1*, *KCNJ11*, *NAMPT*, *UCP2*, *MDR1*, *NeuroD1*, and *PAX4* [168–174]. Among them, *SLCO1B1* is mainly expressed in the basolateral membrane of hepatocytes and can facilitate hepatic uptake of repaglinide [175]; polymorphisms of this gene have significant influence on the pharmacokinetics of repaglinide with reduced pharmacokinetic exposure after a single oral dose administration of 2 mg repaglinide [176]. Thiazolidinediones, also known as glitazones, act as agonists for their molecular target, peroxisome proliferator-activated receptor- γ (PPAR- γ). The direct antioxidant action of glitazones may contribute to its effect on insulin resistance [177]. Recent studies have also reported several loci involved in the pharmacogenetics of thiazolidinediones, including *PGC-1 α* , resistin, adiponectin, leptin, TNF- α , and *CYP2C8* [178–183].

Pharmacogenetic research provides a means to better understand and improve pharmacotherapy. Despite all these advances in the field of pharmacogenetics, adequately designed and rigorously conducted clinical trials are still needed for guiding therapeutic decisions in T2D treatment.

6. Conclusion

To date, approximately 70 loci associated with T2D have been identified. Despite this excellent progress, the current knowledge from these genetic data is still not sufficient to support the clinical utility for the prediction, early identification, and prevention of diabetes. As an emerging field, pharmacogenomics aims at exploring possible molecular mechanisms of drugs and specific genetic variants associated with drug efficacy and thus can make contributions for decisions regarding drug selection, dose titration, treatment duration, and avoidance of adverse drug reactions. However, the loci identified so far explain only a small amount of the estimated heritability of type 2 diabetes and the clinical utility of genetic information is still in its preliminary stage. There is no doubt that intensive studies should be conducted to further identify T2D inheritability factors and promote the translation of novel findings from GWAS to clinical application.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Xue Sun and Weihui Yu contributed equally to this paper.

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References

- [1] J. E. Shaw, R. A. Sicree, and P. Z. Zimmet, "Global estimates of the prevalence of diabetes for 2010 and 2030," *Diabetes Research and Clinical Practice*, vol. 87, no. 1, pp. 4–14, 2010.
- [2] J. B. Meigs, P. Shrader, L. M. Sullivan et al., "Genotype score in addition to common risk factors for prediction of type 2 diabetes," *The New England Journal of Medicine*, vol. 359, no. 21, pp. 2208–2219, 2008.
- [3] M. van Hoek, A. Dehghan, J. C. M. Witteman et al., "Predicting type 2 diabetes based on polymorphisms from genome-wide association studies: a population-based study," *Diabetes*, vol. 57, no. 11, pp. 3122–3128, 2008.
- [4] M. C. Cornelis, L. Qi, C. Zhang et al., "Joint effects of common genetic variants on the risk for type 2 diabetes in US men and women of European ancestry," *Annals of Internal Medicine*, vol. 150, no. 8, pp. 541–550, 2009.
- [5] V. Lyssenko, A. Jonsson, P. Almgren et al., "Clinical risk factors, DNA variants, and the development of type 2 diabetes," *The New England Journal of Medicine*, vol. 359, no. 21, pp. 2220–2232, 2008.
- [6] V. G. Manolopoulos, G. Ragia, and A. Tavridou, "Pharmacogenomics of oral antidiabetic medications: current data and pharmacoepigenomic perspective," *Pharmacogenomics*, vol. 12, no. 8, pp. 1161–1191, 2011.
- [7] C. Huang and J. C. Florez, "Pharmacogenetics in type 2 diabetes: potential implications for clinical practice," *Genome Medicine*, vol. 3, no. 11, article 76, 2011.
- [8] D. Altshuler, J. N. Hirschhorn, M. Klannemark et al., "The common PPAR γ Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes," *Nature Genetics*, vol. 26, no. 1, pp. 76–80, 2000.
- [9] A. L. Gloyn, M. N. Weedon, K. R. Owen et al., "Large-scale association studies of variants in genes encoding the pancreatic β -cell K_{ATP} channel subunits Kir6.2 (*KCNJ11*) and SUR1 (*ABCC8*) confirm that the *KCNJ11* E23K variant is associated with type 2 diabetes," *Diabetes*, vol. 52, no. 2, pp. 568–572, 2003.
- [10] S. F. A. Grant, G. Thorleifsson, I. Reynisdottir et al., "Variant of transcription factor 7-like 2 (*TCF7L2*) gene confers risk of type 2 diabetes," *Nature Genetics*, vol. 38, no. 3, pp. 320–323, 2006.
- [11] M. S. Sandhu, M. N. Weedon, K. A. Fawcett et al., "Common variants in *WFS1* confer risk of type 2 diabetes," *Nature Genetics*, vol. 39, no. 8, pp. 951–953, 2007.
- [12] J. Gudmundsson, P. Sulem, V. Steinthorsdottir et al., "Two variants on chromosome 17 confer prostate cancer risk, and the one in *TCF2* protects against type 2 diabetes," *Nature Genetics*, vol. 39, no. 8, pp. 977–983, 2007.
- [13] E. Zeggini, M. N. Weedon, C. M. Lindgren et al., "Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes," *Science*, vol. 316, no. 5829, pp. 1336–1341, 2007.
- [14] R. Saxena, B. F. Voight, V. Lyssenko et al., "Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels," *Science*, vol. 316, no. 5829, pp. 1331–1336, 2007.
- [15] L. J. Scott, K. L. Mohlke, L. L. Bonnycastle et al., "A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants," *Science*, vol. 316, no. 5829, pp. 1341–1345, 2007.
- [16] V. Steinthorsdottir, G. Thorleifsson, I. Reynisdottir et al., "A variant in *CDKAL1* influences insulin response and risk of type 2 diabetes," *Nature Genetics*, vol. 39, no. 6, pp. 770–775, 2007.
- [17] R. Sladek, G. Rocheleau, J. Rung et al., "A genome-wide association study identifies novel risk loci for type 2 diabetes," *Nature*, vol. 445, no. 7130, pp. 881–885, 2007.
- [18] P. R. Burton, D. G. Clayton, L. R. Cardon et al., "Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls," *Nature*, vol. 447, no. 7145, pp. 661–678, 2007.
- [19] E. Zeggini, L. J. Scott, R. Saxena, and B. F. Voight, "Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes," *Nature Genetics*, vol. 40, no. 5, pp. 638–645, 2008.
- [20] N. Bouatia-Naji, A. Bonnefond, C. Cavalcanti-Proença et al., "A variant near *MTNR1B* is associated with increased fasting plasma glucose levels and type 2 diabetes risk," *Nature Genetics*, vol. 41, no. 1, pp. 89–94, 2009.
- [21] J. Rung, S. Cauchi, A. Albrechtsen et al., "Genetic variant near *IRS1* is associated with type 2 diabetes, insulin resistance and hyperinsulinemia," *Nature Genetics*, vol. 41, no. 10, pp. 1110–1115, 2009.
- [22] J. Dupuis, C. Langenberg, I. Prokopenko et al., "New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk," *Nature Genetics*, vol. 42, no. 2, pp. 105–116, 2010.
- [23] L. Qi, M. C. Cornelis, P. Kraft et al., "Genetic variants at 2q24 are associated with susceptibility to type 2 diabetes," *Human Molecular Genetics*, vol. 19, no. 13, pp. 2706–2715, 2010.
- [24] B. F. Voight, L. J. Scott, V. Steinthorsdottir et al., "Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis," *Nature Genetics*, vol. 42, no. 7, pp. 579–589, 2010.
- [25] A. P. Morris, B. F. Voight, T. M. Teslovich et al., "Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes," *Nature Genetics*, vol. 44, no. 9, pp. 981–990, 2012.
- [26] C. Hu, C. Wang, R. Zhang et al., "Variations in *KCNQ1* are associated with type 2 diabetes and beta cell function in a Chinese population," *Diabetologia*, vol. 52, no. 7, pp. 1322–1325, 2009.

- [27] T. Yamauchi, K. Hara, S. Maeda et al., "A genome-wide association study in the Japanese population identifies susceptibility loci for type 2 diabetes at *UBE2E2* and *C2CD4A-C2CD4B*," *Nature Genetics*, vol. 42, no. 10, pp. 864–868, 2010.
- [28] X. O. Shu, J. Long, Q. Cai et al., "Identification of new genetic risk variants for type 2 diabetes," *PLoS Genetics*, vol. 6, no. 9, Article ID e1001127, 2010.
- [29] F.-J. Tsai, C.-F. Yang, C.-C. Chen et al., "A genome-wide association study identifies susceptibility variants for type 2 diabetes in Han Chinese," *PLoS Genetics*, vol. 6, no. 2, Article ID e1000847, 2010.
- [30] Y. S. Cho, C. H. Chen, C. Hu et al., "Meta-analysis of genome-wide association studies identifies eight new loci for type 2 diabetes in east Asians," *Nature Genetics*, vol. 44, no. 1, pp. 67–72, 2012.
- [31] M. Imamura, S. Maeda, T. Yamauchi et al., "A single-nucleotide polymorphism in *ANKK1* is associated with susceptibility to type 2 diabetes in Japanese populations," *Human Molecular Genetics*, vol. 21, no. 13, pp. 3042–3049, 2012.
- [32] H. Li, W. Gan, L. Lu et al., "A genome-wide association study identifies *GRK5* and *RASGRP1* as type 2 diabetes loci in Chinese Hans," *Diabetes*, vol. 62, no. 1, pp. 291–298, 2013.
- [33] R. C. Ma, C. Hu, C. H. Tam et al., "Genome-wide association study in a Chinese population identifies a susceptibility locus for type 2 diabetes at 7q32 near *PAX4*," *Diabetologia*, vol. 56, no. 6, pp. 1291–1305, 2013.
- [34] K. Hara, H. Fujita, T. A. Johnson et al., "Genome-wide association study identifies three novel loci for type 2 diabetes," *Human Molecular Genetics*, vol. 23, no. 1, pp. 239–246, 2014.
- [35] J. S. Kooner, D. Saleheen, X. Sim et al., "Genome-wide association study in individuals of South Asian ancestry identifies six new type 2 diabetes susceptibility loci," *Nature Genetics*, vol. 43, no. 10, pp. 984–989, 2011.
- [36] R. Tabassum, G. Chauhan, O. P. Dwivedi et al., "Genome-wide association study for type 2 diabetes in Indians identifies a new susceptibility locus at 2q21," *Diabetes*, vol. 62, no. 3, pp. 977–986, 2013.
- [37] R. Saxena, D. Saleheen, L. F. Been et al., "Genome-wide association study identifies a novel locus contributing to type 2 diabetes susceptibility in Sikhs of Punjabi origin from India," *Diabetes*, vol. 62, no. 5, pp. 1746–1755, 2013.
- [38] S. S. Fajans, G. I. Bell, and K. S. Polonsky, "Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young," *The New England Journal of Medicine*, vol. 345, no. 13, pp. 971–980, 2001.
- [39] I. Barroso, "Genetics of type 2 diabetes," *Diabetic Medicine*, vol. 22, no. 5, pp. 517–535, 2005.
- [40] M. Vaxillaire and P. Froguel, "Monogenic diabetes in the young, pharmacogenetics and relevance to multifactorial forms of type 2 diabetes," *Endocrine Reviews*, vol. 29, no. 3, pp. 254–264, 2008.
- [41] Y. Horikawa, N. Oda, N. J. Cox et al., "Genetic variation in the gene encoding calpain-10 is associated with type 2 diabetes mellitus," *Nature Genetics*, vol. 26, no. 2, pp. 163–175, 2000.
- [42] D. Meyre, N. Bouatia-Naji, A. Tounian et al., "Variants of *ENPP1* are associated with childhood and adult obesity and increase the risk of glucose intolerance and type 2 diabetes," *Nature Genetics*, vol. 37, no. 8, pp. 863–867, 2005.
- [43] L. D. Love-Gregory, J. Wasson, J. Ma et al., "A common polymorphism in the upstream promoter region of the hepatocyte nuclear factor-4 α gene on chromosome 20 q is associated with type 2 diabetes and appears to contribute to the evidence for linkage in an Ashkenazi Jewish population," *Diabetes*, vol. 53, no. 4, pp. 1134–1140, 2004.
- [44] K. Silander, K. L. Mohlke, L. J. Scott et al., "Genetic variation near the hepatocyte nuclear factor-4 α gene predicts susceptibility to type 2 diabetes," *Diabetes*, vol. 53, no. 4, pp. 1141–1149, 2004.
- [45] F. Vasseur, N. Helbecque, C. Dina et al., "Single-nucleotide polymorphism haplotypes in the both proximal promoter and exon 3 of the *APM1* gene modulate adipocyte-secreted adiponectin hormone levels and contribute to the genetic risk for type 2 diabetes in French Caucasians," *Human Molecular Genetics*, vol. 11, no. 21, pp. 2607–2614, 2002.
- [46] S. S. Deeb, L. Fajas, M. Nemoto et al., "A Pro12Ala substitution in *PPAR γ 2* associated with decreased receptor activity, lower body mass index and improved insulin sensitivity," *Nature Genetics*, vol. 20, no. 3, pp. 284–287, 1998.
- [47] A. Karasik, C. O'Hara, S. Srikanta et al., "Genetically programmed selective islet β -cell loss in diabetic subjects with Wolfram's syndrome," *Diabetes Care*, vol. 12, no. 2, pp. 135–138, 1989.
- [48] A. C. Riggs, E. Bernal-Mizrachi, M. Ohsugi et al., "Mice conditionally lacking the Wolfram gene in pancreatic islet beta cells exhibit diabetes as a result of enhanced endoplasmic reticulum stress and apoptosis," *Diabetologia*, vol. 48, no. 11, pp. 2313–2321, 2005.
- [49] T. Yamada, H. Ishihara, A. Tamura et al., "WFS1-deficiency increases endoplasmic reticulum stress, impairs cell cycle progression and triggers the apoptotic pathway specifically in pancreatic β -cells," *Human Molecular Genetics*, vol. 15, no. 10, pp. 1600–1609, 2006.
- [50] C. J. Groves, E. Zeggini, J. Minton et al., "Association analysis of 6,736 UK subjects provides replication and confirms *TCF7L2* as a type 2 diabetes susceptibility gene with a substantial effect on individual risk," *Diabetes*, vol. 55, no. 9, pp. 2640–2644, 2006.
- [51] C. Zhang, L. Qi, D. J. Hunter et al., "Variant of transcription factor 7-like 2 (*TCF7L2*) gene and the risk of type 2 diabetes in large cohorts of US women and men," *Diabetes*, vol. 55, no. 9, pp. 2645–2648, 2006.
- [52] L. J. Scott, L. L. Bonnycastle, C. J. Willer et al., "Association of transcription factor 7-like 2 (*TCF7L2*) variants with type 2 diabetes in a Finnish sample," *Diabetes*, vol. 55, no. 9, pp. 2649–2653, 2006.
- [53] C. M. Damcott, T. I. Pollin, L. J. Reinhart et al., "Polymorphisms in the transcription factor 7-like 2 (*TCF7L2*) gene are associated with type 2 diabetes in the Amish: replication and evidence for a role in both insulin secretion and insulin resistance," *Diabetes*, vol. 55, no. 9, pp. 2654–2659, 2006.
- [54] R. Saxena, L. Gianniny, N. P. Burt et al., "Common single nucleotide polymorphisms in *TCF7L2* are reproducibly associated with type 2 diabetes and reduce the insulin response to glucose in nondiabetic individuals," *Diabetes*, vol. 55, no. 10, pp. 2890–2895, 2006.
- [55] S. Cauchi, D. Meyre, C. Dina et al., "Transcription factor *TCF7L2* genetic study in the French population: expression in human β -cells and adipose tissue and strong association with type 2 diabetes," *Diabetes*, vol. 55, no. 10, pp. 2903–2908, 2006.
- [56] T. Hayashi, Y. Iwamoto, K. Kaku, H. Hirose, and S. Maeda, "Replication study for the association of *TCF7L2* with susceptibility to type 2 diabetes in a Japanese population," *Diabetologia*, vol. 50, no. 5, pp. 980–984, 2007.
- [57] M. Horikoshi, K. Hara, C. Ito, R. Nagai, P. Froguel, and T. Kadowaki, "A genetic variation of the transcription factor 7-like

- 2 gene is associated with risk of type 2 diabetes in the Japanese population," *Diabetologia*, vol. 50, no. 4, pp. 747–751, 2007.
- [58] A. C. Foley and M. Mercola, "Heart induction by Wnt antagonists depends on the homeodomain transcription factor Hex," *Genes & Development*, vol. 19, no. 3, pp. 387–396, 2005.
- [59] A. M. Simonis-Bik, G. Nijpels, T. W. van Haeften et al., "Gene variants in the novel type 2 diabetes loci *CDC123/CAMK1D*, *THADA*, *ADAMTS9*, *BCL11A*, and *MTNR1B* affect different aspects of pancreatic β -cell function," *Diabetes*, vol. 59, no. 1, pp. 293–301, 2010.
- [60] N. Grarup, G. Andersen, N. T. Krarup et al., "Association testing of novel type 2 diabetes risk alleles in the *JAZF1*, *CDC123/CAMK1D*, *TSPAN8*, *THADA*, *ADAMTS9*, and *NOTCH2* Loci with insulin release, insulin sensitivity, and obesity in a population-based sample of 4,516 glucose-tolerant middle-aged danes," *Diabetes*, vol. 57, no. 9, pp. 2534–2540, 2008.
- [61] I. Prokopenko, C. Langenberg, J. C. Florez et al., "Variants in *MTNR1B* influence fasting glucose levels," *Nature Genetics*, vol. 41, no. 1, pp. 77–81, 2009.
- [62] J. S. Willson, T. D. Godwin, G. A. Wiggins et al., "Primary hepatocellular neoplasms in a *MODY3* family with a novel *HNF1A* germline mutation," *Journal of Hepatology*, vol. 59, no. 4, pp. 904–907, 2013.
- [63] D. M. Lim, N. Huh, and K. Y. Park, "Hepatocyte nuclear factor 1- α mutation in normal glucose-tolerant subjects and early-onset type 2 diabetic patients," *Korean Journal of Internal Medicine*, vol. 23, no. 4, pp. 165–169, 2008.
- [64] R. A. Hegele, H. Cao, S. B. Harris, A. J. G. Hanley, and B. Zinman, "The hepatic nuclear factor-1 α G319S variant is associated with early-onset type 2 diabetes in Canadian Ojibwe," *The Journal of Clinical Endocrinology & Metabolism*, vol. 84, no. 3, pp. 1077–1082, 1999.
- [65] H. Xu, M. Dembski, Q. Yang et al., "Dual specificity mitogen-activated protein (MAP) kinase phosphatase-4 plays a potential role in insulin resistance," *The Journal of Biological Chemistry*, vol. 278, no. 32, pp. 30187–30192, 2003.
- [66] M. Bazuine, F. Carlotti, R. S. Tafrechi, R. C. Hoeben, and J. A. Maassen, "Mitogen-activated protein kinase (MAPK) phosphatase-1 and -4 attenuate p38 MAPK during dexamethasone-induced insulin resistance in 3T3-L1 adipocytes," *Molecular Endocrinology*, vol. 18, no. 7, pp. 1697–1707, 2004.
- [67] B. Emanuelli, D. Eberlé, R. Suzuki, and C. R. Kahn, "Overexpression of the dual-specificity phosphatase MKP-4/DUSP-9 protects against stress-induced insulin resistance," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 9, pp. 3545–3550, 2008.
- [68] M. N. Harder, R. Ribel-Madsen, J. M. Justesen et al., "Type 2 diabetes risk alleles near *BCAR1* and in *ANK1* associate with decreased β -cell function whereas risk alleles near *ANKRD55* and *GRB14* associate with decreased insulin sensitivity in the Danish Inter99 cohort," *The Journal of Clinical Endocrinology & Metabolism*, vol. 98, no. 4, pp. E801–E806, 2013.
- [69] H. Li, B. Oldenburg, C. Chamberlain et al., "Diabetes prevalence and determinants in adults in China mainland from 2000 to 2010: a systematic review," *Diabetes Research and Clinical Practice*, vol. 98, no. 2, pp. 226–235, 2012.
- [70] K. Yasuda, K. Miyake, Y. Horikawa et al., "Variants in *KCNQ1* are associated with susceptibility to type 2 diabetes mellitus," *Nature Genetics*, vol. 40, no. 9, pp. 1092–1097, 2008.
- [71] H. Unoki, A. Takahashi, T. Kawaguchi et al., "SNPs in *KCNQ1* are associated with susceptibility to type 2 diabetes in East Asian and European populations," *Nature Genetics*, vol. 40, no. 9, pp. 1098–1102, 2008.
- [72] Y.-H. Lee, E. S. Kang, S. H. Kim et al., "Association between polymorphisms in *SLC30A8*, *HHEX*, *CDKN2A/B*, *IGF2BP2*, *FTO*, *WFS1*, *CDKAL1*, *KCNQ1* and type 2 diabetes in the Korean population," *Journal of Human Genetics*, vol. 53, no. 11–12, pp. 991–998, 2008.
- [73] J. T. Tan, S. Nurbaya, D. Gardner, S. Ye, E. S. Tai, and D. P. K. Ng, "Genetic variation in *KCNQ1* associates with fasting glucose and β -cell function: a study of 3,734 subjects comprising three ethnicities living in Singapore," *Diabetes*, vol. 58, no. 6, pp. 1445–1449, 2009.
- [74] K. Müsigg, H. Staiger, F. Machicao et al., "Association of type 2 diabetes candidate polymorphisms in *KCNQ1* with incretin and insulin secretion," *Diabetes*, vol. 58, no. 7, pp. 1715–1720, 2009.
- [75] Y. C. Chang, Y. F. Chiu, P. H. Liu et al., "Replication of genome-wide association signals of type 2 diabetes in Han Chinese in a prospective cohort," *Clinical Endocrinology*, vol. 76, no. 3, pp. 365–372, 2012.
- [76] H. Wolosker, S. Blackshaw, and S. H. Snyder, "Serine racemase: a glial enzyme synthesizing D-serine to regulate glutamate-N-methyl-D-aspartate neurotransmission," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 23, pp. 13409–13414, 1999.
- [77] H. Wolosker, K. N. Sheth, M. Takahashi et al., "Purification of serine racemase: biosynthesis of the neuromodulator D-serine," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 2, pp. 721–725, 1999.
- [78] N. Soranzo, S. Sanna, E. Wheeler et al., "Common variants at 10 genomic loci influence hemoglobin A_{1C} levels via glycemic and nonglycemic pathways," *Diabetes*, vol. 59, no. 12, pp. 3229–3239, 2010.
- [79] L. Wang, M. Shen, F. Wang et al., "GRK5 ablation contributes to insulin resistance," *Biochemical and Biophysical Research Communications*, vol. 429, no. 1–2, pp. 99–104, 2012.
- [80] J. Wang, L. Elghazi, S. E. Parker et al., "The concerted activities of *PAX4* and *Nkx2.2* are essential to initiate pancreatic β -cell differentiation," *Developmental Biology*, vol. 266, no. 1, pp. 178–189, 2004.
- [81] Y. Zhang, R. Proenca, M. Maffei, M. Barone, L. Leopold, and J. M. Friedman, "Positional cloning of the mouse obese gene and its human homologue," *Nature*, vol. 372, no. 6505, pp. 425–432, 1994.
- [82] Y. Liu, L. Yu, D. Zhang et al., "Positive association between variations in *CDKAL1* and type 2 diabetes in Han Chinese individuals," *Diabetologia*, vol. 51, no. 11, pp. 2134–2137, 2008.
- [83] M. Xu, Y. Bi, Y. Xu et al., "Combined effects of 19 common variations on type 2 diabetes in Chinese: results from two community-based studies," *PLoS ONE*, vol. 5, no. 11, Article ID e14022, 2010.
- [84] Y. Wu, H. Li, R. J. F. Loos et al., "Common variants in *CDKAL1*, *CDKN2A/B*, *IGF2BP2*, *SLC30A8*, and *HHEX/IDE* genes are associated with type 2 diabetes and impaired fasting glucose in a Chinese Han population," *Diabetes*, vol. 57, no. 10, pp. 2834–2842, 2008.
- [85] Y. Liu, Z. Liu, Y. Song et al., "Meta-analysis added power to identify variants in *FTO* associated with type 2 diabetes and obesity in the Asian population," *Obesity*, vol. 18, no. 8, pp. 1619–1624, 2010.

- [86] J. Wen, T. Rönn, A. Olsson et al., "Investigation of type 2 diabetes risk alleles support *CDKN2A/B*, *CDKAL1*, and *TCF7L2* as susceptibility genes in a Han Chinese cohort," *PLoS ONE*, vol. 5, no. 2, Article ID e9153, 2010.
- [87] C. Hu, R. Zhang, C. Wang et al., "*PPARG*, *KCNJ11*, *CDKAL1*, *CDKN2A-CDKN2B*, *IDE-KIF11-HHEX*, *IGF2BP2* and *SLC30A8* are associated with type 2 diabetes in a Chinese population," *PLoS ONE*, vol. 4, no. 10, Article ID e7643, 2009.
- [88] J. Xiang, X.-Y. Li, M. Xu et al., "Zinc transporter-8 gene (*SLC30A8*) is associated with type 2 diabetes in Chinese," *The Journal of Clinical Endocrinology & Metabolism*, vol. 93, no. 10, pp. 4107–4112, 2008.
- [89] T. Rönn, J. Wen, Z. Yang et al., "A common variant in *MTNR1B*, encoding melatonin receptor 1B, is associated with type 2 diabetes and fasting plasma glucose in Han Chinese individuals," *Diabetologia*, vol. 52, no. 5, pp. 830–833, 2009.
- [90] M. C. Y. Ng, C. H. T. Tam, V. K. L. Lam, W.-Y. So, R. C. W. Ma, and J. C. N. Chan, "Replication and identification of novel variants at *TCF7L2* associated with type 2 diabetes in Hong Kong Chinese," *The Journal of Clinical Endocrinology & Metabolism*, vol. 92, no. 9, pp. 3733–3737, 2007.
- [91] M. C. Y. Ng, K. S. Park, B. Oh et al., "Implication of genetic variants near *TCF7L2*, *SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2A/B*, *IGF2BP2*, and *FTO* in type 2 diabetes and obesity in 6,719 Asians," *Diabetes*, vol. 57, no. 8, pp. 2226–2233, 2008.
- [92] Y.-C. Chang, T.-J. Chang, Y.-D. Jiang et al., "Association study of the genetic polymorphisms of the transcription factor 7-like 2 (*TCF7L2*) gene and type 2 diabetes in the Chinese population," *Diabetes*, vol. 56, no. 10, pp. 2631–2637, 2007.
- [93] H. Fukuda, M. Imamura, Y. Tanaka et al., "A single nucleotide polymorphism within *DUSP9* is associated with susceptibility to type 2 diabetes in a Japanese population," *PLoS One*, vol. 7, no. 9, Article ID e46263, 2012.
- [94] B. Basnyat and L. C. Rajapaksa, "Cardiovascular and infectious diseases in South Asia: the double whammy," *British Medical Journal*, vol. 328, no. 7443, p. 781, 2004.
- [95] R. M. Anjana, R. Pradeepa, M. Deepa et al., "Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: phase i results of the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study," *Diabetologia*, vol. 54, no. 12, pp. 3022–3027, 2011.
- [96] A. Ramachandran, R. C. Ma, and C. Snehalatha, "Diabetes in Asia," *The Lancet*, vol. 375, no. 9712, pp. 408–418, 2010.
- [97] J. C. Chambers, O. A. Obeid, H. Refsum et al., "Plasma homocysteine concentrations and risk of coronary heart disease in UK Indian Asian and European men," *The Lancet*, vol. 355, no. 9203, pp. 523–527, 2000.
- [98] D. K. Sanghera, L. Ortega, S. Han et al., "Impact of nine common type 2 diabetes risk polymorphisms in Asian Indian Sikhs: *PPARG2* (*Pro12Ala*), *IGF2BP2*, *TCF7L2* and *FTO* variants confer a significant risk," *BMC Medical Genetics*, vol. 9, article 59, 2008.
- [99] C. S. Yajnik, C. S. Janipalli, S. Bhaskar et al., "*FTO* gene variants are strongly associated with type 2 diabetes in South Asian Indians," *Diabetologia*, vol. 52, no. 2, pp. 247–252, 2009.
- [100] M. Chidambaram, V. Radha, and V. Mohan, "Replication of recently described type 2 diabetes gene variants in a South Indian population," *Metabolism*, vol. 59, no. 12, pp. 1760–1766, 2010.
- [101] G. Chauhan, C. J. Spurgeon, R. Tabassum et al., "Impact of common variants of *PPARG*, *KCNJ11*, *TCF7L2*, *SLC30A8*, *HHEX*, *CDKN2A*, *IGF2BP2*, and *CDKAL1* on the risk of type 2 diabetes in 5,164 Indians," *Diabetes*, vol. 59, no. 8, pp. 2068–2074, 2010.
- [102] S. D. Rees, M. Z. I. Hydrie, A. S. Shera et al., "Replication of 13 genome-wide association (GWA)-validated risk variants for type 2 diabetes in Pakistani populations," *Diabetologia*, vol. 54, no. 6, pp. 1368–1374, 2011.
- [103] L. Ma, R. L. Hanson, L. N. Que et al., "Variants in *ARHGEF11*, a candidate gene for the linkage to type 2 diabetes on chromosome 1q, are nominally associated with insulin resistance and type 2 diabetes in Pima Indians," *Diabetes*, vol. 56, no. 5, pp. 1454–1459, 2007.
- [104] L. Ma, R. L. Hanson, L. N. Que et al., "*PCLO* variants are nominally associated with early-onset type 2 diabetes and insulin resistance in Pima Indians," *Diabetes*, vol. 57, no. 11, pp. 3156–3160, 2008.
- [105] L. Bian, R. L. Hanson, Y. L. Muller et al., "Variants in *ACAD10* are associated with type 2 diabetes, insulin resistance and lipid oxidation in Pima Indians," *Diabetologia*, vol. 53, no. 7, pp. 1349–1353, 2010.
- [106] L. Bian, R. L. Hanson, V. Ossowski et al., "Variants in *ASK1* are associated with skeletal muscle *ASK1* expression, in vivo insulin resistance, and type 2 diabetes in Pima Indians," *Diabetes*, vol. 59, no. 5, pp. 1276–1282, 2010.
- [107] R. Rong, R. L. Hanson, D. Ortiz et al., "Association analysis of variation in/near *FTO*, *CDKAL1*, *SLC30A8*, *HHEX*, *EXT2*, *IGF2BP2*, *LOC387761*, and *CDKN2B* with type 2 diabetes and related quantitative traits in Pima Indians," *Diabetes*, vol. 58, no. 2, pp. 478–488, 2009.
- [108] M. G. Hayes, A. Pluzhnikov, K. Miyake et al., "Identification of type 2 diabetes genes in Mexican Americans through genome-wide association studies," *Diabetes*, vol. 56, no. 12, pp. 3033–3044, 2007.
- [109] J. E. Below, E. R. Gamazon, J. V. Morrison et al., "Genome-wide association and meta-analysis in populations from Starr County, Texas, and Mexico City identify type 2 diabetes susceptibility loci and enrichment for expression quantitative trait loci in top signals," *Diabetologia*, vol. 54, no. 8, pp. 2047–2055, 2011.
- [110] "Sequence variants in *SLC16A11* are a common risk factor for type 2 diabetes in Mexico," *Nature*, vol. 506, pp. 97–101, 2013.
- [111] V. Lyssenko, C. L. F. Nagorny, M. R. Erdos et al., "Common variant in *MTNR1B* associated with increased risk of type 2 diabetes and impaired early insulin secretion," *Nature Genetics*, vol. 41, no. 1, pp. 82–88, 2009.
- [112] T. W. Boesgaard, N. Grarup, T. Jørgensen, K. Borch-Johnsen, T. Hansen, and O. Pedersen, "Variants at *DGKB/TMEM195*, *ADRA2A*, *GLIS3* and *C2CD4B* loci are associated with reduced glucose-stimulated beta cell function in middle-aged Danish people," *Diabetologia*, vol. 53, no. 8, pp. 1647–1655, 2010.
- [113] T. Nielsen, T. Sparsø, N. Grarup et al., "Type 2 diabetes risk allele near *CENTD2* is associated with decreased glucose-stimulated insulin release," *Diabetologia*, vol. 54, no. 5, pp. 1052–1056, 2011.
- [114] S. D. Rees, M. Z. I. Hydrie, J. P. O'Hare et al., "Effects of 16 genetic variants on fasting glucose and type 2 diabetes in South Asians: *ADCY5* and *GLIS3* variants may predispose to type 2 diabetes," *PLoS ONE*, vol. 6, no. 9, Article ID e24710, 2011.
- [115] T. W. Boesgaard, A. P. Gjesing, N. Grarup et al., "Variant near *ADAMTS9* known to associate with type 2 diabetes is related to insulin resistance in offspring of type 2 diabetes patients—EUGENE2 study," *PLoS ONE*, vol. 4, no. 9, Article ID e7236, 2009.

- [116] A. Anand and K. Chada, "In vivo modulation of *Hmgic* reduces obesity," *Nature Genetics*, vol. 24, no. 4, pp. 377–380, 2000.
- [117] T. Q. Binh, P. T. Phuong, B. T. Nhung et al., "Association of the common *FTO*-rs9939609 polymorphism with type 2 diabetes, independent of obesity-related traits in a Vietnamese population," *Gene*, vol. 513, no. 1, pp. 31–35, 2013.
- [118] B. Xi, F. Takeuchi, G. R. Chandak et al., "Common polymorphism near the *MC4R* gene is associated with type 2 diabetes: data from a meta-analysis of 123, 373 individuals," *Diabetologia*, vol. 55, no. 10, pp. 2660–2666, 2012.
- [119] V. Lyssenko, R. Lupi, P. Marchetti et al., "Mechanisms by which common variants in the *TCF7L2* gene increase risk of type 2 diabetes," *The Journal of Clinical Investigation*, vol. 117, no. 8, pp. 2155–2163, 2007.
- [120] D. T. Villareal, H. Robertson, G. I. Bell et al., "*TCF7L2* variant rs7903146 affects the risk of type 2 diabetes by modulating incretin action," *Diabetes*, vol. 59, no. 2, pp. 479–485, 2010.
- [121] O. le Bacquer, J. Kerr-Conte, S. Gargani et al., "*TCF7L2* rs7903146 impairs islet function and morphology in non-diabetic individuals," *Diabetologia*, vol. 55, no. 10, pp. 2677–2681, 2012.
- [122] Y. Takeda, Y. Fujita, J. Honjo et al., "Reduction of both β cell death and alpha cell proliferation by dipeptidyl peptidase-4 inhibition in a streptozotocin-induced model of diabetes in mice," *Diabetologia*, vol. 55, no. 2, pp. 404–412, 2012.
- [123] K. H. Yoon, S. H. Ko, J. H. Cho et al., "Selective β -cell loss and α -cell expansion in patients with type 2 diabetes mellitus in Korea," *The Journal of Clinical Endocrinology & Metabolism*, vol. 88, no. 5, pp. 2300–2308, 2003.
- [124] C. L. Kirkpatrick, P. Marchetti, F. Purrello et al., "Type 2 diabetes susceptibility gene expression in normal or diabetic sorted human alpha and beta cells: correlations with age or BMI of islet donors," *PLoS ONE*, vol. 5, no. 6, Article ID e11053, 2010.
- [125] V. Korinek, N. Barker, P. Moerer et al., "Depletion of epithelial stem-cell compartments in the small intestine of mice lacking Tcf-4," *Nature Genetics*, vol. 19, no. 4, pp. 379–383, 1998.
- [126] W. Ip, Y. T. Chiang, and T. Jin, "The involvement of the Wnt signaling pathway and *TCF7L2* in diabetes mellitus: the current understanding, dispute, and perspective," *Cell & Bioscience*, vol. 2, no. 1, article 28, 2012.
- [127] J. Dessimoz, C. Bonnard, J. Huelsken, and A. Grapin-Botton, "Pancreas-specific deletion of β -catenin reveals Wnt-dependent and Wnt-independent functions during development," *Current Biology*, vol. 15, no. 18, pp. 1677–1683, 2005.
- [128] L. C. Murtaugh, A. C. Law, Y. Dor, and D. A. Melton, " β -catenin is essential for pancreatic acinar but not islet development," *Development*, vol. 132, no. 21, pp. 4663–4674, 2005.
- [129] S. Papadopoulou and H. Edlund, "Attenuated Wnt signaling perturbs pancreatic growth but not pancreatic function," *Diabetes*, vol. 54, no. 10, pp. 2844–2851, 2005.
- [130] P. W. Heiser, J. Lau, M. M. Taketo, P. L. Herrera, and M. Hebrok, "Stabilization of β -catenin impacts pancreas growth," *Development*, vol. 133, no. 10, pp. 2023–2032, 2006.
- [131] R. S. Heller, D. S. Dichmann, J. Jensen et al., "Expression patterns of Wnts, Frizzleds, sFRPs, and misexpression in transgenic mice suggesting a role for Wnts in pancreas and foregut pattern formation," *Developmental Dynamics*, vol. 225, no. 3, pp. 260–270, 2002.
- [132] I. C. Rulifson, S. K. Karnik, P. W. Heiser et al., "Wnt signaling regulates pancreatic β cell proliferation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 15, pp. 6247–6252, 2007.
- [133] S. F. Boj, J. H. van Es, M. Huch et al., "Diabetes risk gene and Wnt effector *TCF7L2*/TCF4 controls hepatic response to perinatal and adult metabolic demand," *Cell*, vol. 151, no. 7, pp. 1595–1607, 2012.
- [134] F. Chimienti, A. Favier, and M. Seve, "ZnT-8, a pancreatic β -cell-specific zinc transporter," *Biometals*, vol. 18, no. 4, pp. 313–317, 2005.
- [135] M. Tamaki, Y. Fujitani, T. Uchida, T. Hirose, R. Kawamori, and H. Watada, "Downregulation of ZnT8 expression in pancreatic β -cells of diabetic mice," *Islets*, vol. 1, no. 2, pp. 124–128, 2009.
- [136] L. D. Pound, S. A. Sarkar, R. K. P. Benninger et al., "Deletion of the mouse *Slc30a8* gene encoding zinc transporter-8 results in impaired insulin secretion," *Biochemical Journal*, vol. 421, no. 3, pp. 371–376, 2009.
- [137] M. Tamaki, Y. Fujitani, A. Hara et al., "The diabetes-susceptible gene *SLC30A8*/ZnT8 regulates hepatic insulin clearance," *The Journal of Clinical Investigation*, vol. 123, no. 10, pp. 4513–4524, 2013.
- [138] F. Chimienti, S. Devergnas, F. Pattou et al., "In vivo expression and functional characterization of the zinc transporter ZnT8 in glucose-induced insulin secretion," *Journal of Cell Science*, vol. 119, no. 20, pp. 4199–4206, 2006.
- [139] L. D. Pound, Y. Hang, S. A. Sarkar et al., "The pancreatic islet β -cell-enriched transcription factor Pdx-1 regulates *Slc30a8* gene transcription through an intronic enhancer," *Biochemical Journal*, vol. 433, no. 1, pp. 95–105, 2011.
- [140] Q. Qi and F. B. Hu, "Genetics of type 2 diabetes in European populations," *Journal of Diabetes*, vol. 4, no. 3, pp. 203–212, 2012.
- [141] M. Imamura, D. Shigemizu, T. Tsunoda et al., "Assessing the clinical utility of a genetic risk score constructed using 49 susceptibility alleles for type 2 diabetes in a Japanese population," *The Journal of Clinical Endocrinology & Metabolism*, vol. 98, no. 10, pp. 1667–1673, 2013.
- [142] J. N. Cooke, M. C. Y. Ng, N. D. Palmer et al., "Genetic risk assessment of type 2 diabetes-associated polymorphisms in African Americans," *Diabetes Care*, vol. 35, no. 2, pp. 287–292, 2012.
- [143] M. Iwata, S. Maeda, Y. Kamura et al., "Genetic risk score constructed using 14 susceptibility alleles for type 2 diabetes is associated with the early onset of diabetes and may predict the future requirement of insulin injections among Japanese individuals," *Diabetes Care*, vol. 35, no. 8, pp. 1763–1770, 2012.
- [144] P. J. Talmud, A. D. Hingorani, J. A. Cooper et al., "Utility of genetic and non-genetic risk factors in prediction of type 2 diabetes: Whitehall II prospective cohort study," *British Medical Journal*, vol. 340, Article ID b4838, 2010.
- [145] J. M. de Miguel-Yanes, P. Shrader, M. J. Pencina et al., "Genetic risk reclassification for type 2 diabetes by age below or above 50 years using 40 type 2 diabetes risk single nucleotide polymorphisms," *Diabetes Care*, vol. 34, no. 1, pp. 121–125, 2011.
- [146] M. C. Cornelis and F. B. Hu, "Gene-environment interactions in the development of type 2 diabetes: recent progress and continuing challenges," *Annual Review of Nutrition*, vol. 32, pp. 245–259, 2012.
- [147] L. Wang, H. L. McLeod, and R. M. Weinshilboum, "Genomics and drug response," *The New England Journal of Medicine*, vol. 364, no. 12, pp. 1144–1153, 2011.
- [148] G. C. Mannino and G. Sesti, "Individualized therapy for type 2 diabetes: clinical implications of pharmacogenetic data," *Molecular Diagnosis & Therapy*, vol. 16, no. 5, pp. 285–302, 2012.

- [149] H. Xu, M. Murray, and A. J. McLachlan, "Influence of genetic polymorphisms on the pharmacokinetics and pharmacodynamics of sulfonylurea drugs," *Current Drug Metabolism*, vol. 10, no. 6, pp. 643–658, 2009.
- [150] A. Surendiran, S. C. Pradhan, A. Agrawal et al., "Influence of CYP2C9 gene polymorphisms on response to glibenclamide in type 2 diabetes mellitus patients," *European Journal of Clinical Pharmacology*, vol. 67, no. 8, pp. 797–801, 2011.
- [151] M. Rafiq, S. E. Flanagan, A.-M. Patch et al., "Effective treatment with oral sulfonylureas in patients with diabetes due to sulfonylurea receptor 1 (SUR1) mutations," *Diabetes Care*, vol. 31, no. 2, pp. 204–209, 2008.
- [152] Y. Feng, G. Mao, X. Ren et al., "Ser1369Ala variant in sulfonylurea receptor gene ABCC8 is associated with antidiabetic efficacy of gliclazide in Chinese type 2 diabetic patients," *Diabetes Care*, vol. 31, no. 10, pp. 1939–1944, 2008.
- [153] E. R. Pearson, L. A. Donnelly, C. Kimber et al., "Variation in TCF7L2 influences therapeutic response to sulfonylureas: a GoDARTs study," *Diabetes*, vol. 56, no. 8, pp. 2178–2182, 2007.
- [154] M. G. García-Escalante, V. M. Suárez-Solís, M. T. D. J. López-Ávila, D. D. C. Pinto-Escalante, and H. Laviada-Molina, "Effect of the Gly972Arg, SNP43 and Pro12Ala polymorphisms of the genes IRS1, CAPN10 and PPARG2 on secondary failure to sulphonylurea and metformin in patients with type 2 diabetes in Yucatán, México," *Investigacion Clinica*, vol. 50, no. 1, pp. 65–76, 2009.
- [155] M. L. Becker, A.-J. Aarnoudse, C. Newton-Cheh et al., "Common variation in the NOS1AP gene is associated with reduced glucose-lowering effect and with increased mortality in users of sulfonylurea," *Pharmacogenetics and Genomics*, vol. 18, no. 7, pp. 591–597, 2008.
- [156] A. Seeringer, S. Parmar, A. Fischer et al., "Genetic variants of the insulin receptor substrate-1 are influencing the therapeutic efficacy of oral antidiabetics," *Diabetes, Obesity and Metabolism*, vol. 12, no. 12, pp. 1106–1112, 2010.
- [157] G. Sesti, M. A. Marini, M. Cardellini et al., "The Arg⁹⁷² variant in insulin receptor substrate-1 is associated with an increased risk of secondary failure to sulfonylurea in patients with type 2 diabetes," *Diabetes Care*, vol. 27, no. 6, pp. 1394–1398, 2004.
- [158] E. R. Pearson, I. Flechtner, P. R. Njolstad et al., "Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations," *The New England Journal of Medicine*, vol. 355, no. 5, pp. 467–477, 2006.
- [159] Y. Shu, S. A. Sheardown, C. Brown et al., "Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action," *The Journal of Clinical Investigation*, vol. 117, no. 5, pp. 1422–1431, 2007.
- [160] M. V. Tzvetkov, S. V. Vormfelde, D. Balen et al., "The effects of genetic polymorphisms in the organic cation transporters OCT1, OCT2, and OCT3 on the renal clearance of metformin," *Clinical Pharmacology & Therapeutics*, vol. 86, no. 3, pp. 299–306, 2009.
- [161] M. L. Becker, L. E. Visser, R. H. N. van Schaik, A. Hofman, A. G. Uitterlinden, and B. H. C. Stricker, "Genetic variation in the organic cation transporter 1 is associated with metformin response in patients with diabetes mellitus," *Pharmacogenomics Journal*, vol. 9, no. 4, pp. 242–247, 2009.
- [162] M. M. H. Christensen, C. Brasch-Andersen, H. Green et al., "The pharmacogenetics of metformin and its impact on plasma metformin steady-state levels and glycosylated hemoglobin A1c," *Pharmacogenetics and Genomics*, vol. 21, no. 12, pp. 837–850, 2011.
- [163] I. S. Song, H. J. Shin, E. J. Shim et al., "Genetic variants of the organic cation transporter 2 influence the disposition of metformin," *Clinical Pharmacology & Therapeutics*, vol. 84, no. 5, pp. 559–562, 2008.
- [164] M. L. Becker, L. E. Visser, R. H. N. van Schaik, A. Hofman, A. G. Uitterlinden, and B. H. C. Stricker, "Genetic variation in the multidrug and toxin extrusion 1 transporter protein influences the glucose-lowering effect of metformin in patients with diabetes: a preliminary study," *Diabetes*, vol. 58, no. 3, pp. 745–749, 2009.
- [165] K. A. Jablonski, J. B. McAtter, P. I. W. de Bakker et al., "Common variants in 40 genes assessed for diabetes incidence and response to metformin and lifestyle intervention in the diabetes prevention program," *Diabetes*, vol. 59, no. 10, pp. 2672–2681, 2010.
- [166] J. H. Choi, S. W. Yee, A. H. Ramirez et al., "A common 5'-UTR variant in MATE2-K is associated with poor response to metformin," *Clinical Pharmacology & Therapeutics*, vol. 90, no. 5, pp. 674–684, 2011.
- [167] K. Zhou, C. Bellenguez, C. C. A. Spencer et al., "Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes," *Nature Genetics*, vol. 43, no. 2, pp. 117–120, 2011.
- [168] J. Kirchheiner, I. Roots, M. Goldammer, B. Rosenkranz, and J. Brockmöller, "Effect of genetic polymorphisms in cytochrome P450 (CYP) 2C9 and CYP2C8 on the pharmacokinetics of oral antidiabetic drugs: clinical relevance," *Clinical Pharmacokinetics*, vol. 44, no. 12, pp. 1209–1225, 2005.
- [169] Y. Cheng, G. Wang, W. Zhang et al., "Effect of CYP2C9 and SLCO1B1 polymorphisms on the pharmacokinetics and pharmacodynamics of nateglinide in healthy Chinese male volunteers," *European Journal of Clinical Pharmacology*, vol. 69, no. 3, pp. 407–413, 2013.
- [170] W. Zhang, Y.-J. He, C.-T. Han et al., "Effect of SLCO1B1 genetic polymorphism on the pharmacokinetics of nateglinide," *British Journal of Clinical Pharmacology*, vol. 62, no. 5, pp. 567–572, 2006.
- [171] Q. Huang, J.-Y. Yin, X.-P. Dai et al., "Association analysis of SLC30A8 rs13266634 and rs16889462 polymorphisms with type 2 diabetes mellitus and repaglinide response in Chinese patients," *European Journal of Clinical Pharmacology*, vol. 66, no. 12, pp. 1207–1215, 2010.
- [172] Q. Xiang, Y. M. Cui, X. Zhao, L. Yan, and Y. Zhou, "The influence of MDR1G2677T/A genetic polymorphisms on the pharmacokinetics of repaglinide in healthy Chinese volunteers," *Pharmacology*, vol. 89, no. 1-2, pp. 105–110, 2012.
- [173] X.-P. Dai, Q. Huang, J.-Y. Yin et al., "KCNQ1 gene polymorphisms are associated with the therapeutic efficacy of repaglinide in Chinese type 2 diabetic patients," *Clinical and Experimental Pharmacology and Physiology*, vol. 39, no. 5, pp. 462–468, 2012.
- [174] F.-F. Sheng, X.-P. Dai, J. Qu et al., "NAMPT-3186C/T polymorphism affects repaglinide response in Chinese patients with type 2 diabetes mellitus," *Clinical and Experimental Pharmacology and Physiology*, vol. 38, no. 8, pp. 550–554, 2011.
- [175] H. Takane, "Genetic polymorphisms of SLCO1B1 for drug pharmacokinetics and its clinical implications," *Yakugaku Zasshi*, vol. 131, no. 11, pp. 1589–1594, 2011.
- [176] J. He, Z. Qiu, N. Li et al., "Effects of SLCO1B1 polymorphisms on the pharmacokinetics and pharmacodynamics of repaglinide in healthy Chinese volunteers," *European Journal of Clinical Pharmacology*, vol. 67, no. 7, pp. 701–707, 2011.

- [177] K. Mizushige, T. Tsuji, and T. Noma, "Pioglitazone: cardiovascular effects in prediabetic patients," *Cardiovascular Drug Reviews*, vol. 20, no. 4, pp. 329–340, 2002.
- [178] E. S. Kang, S. Y. Park, H. J. Kim et al., "Effects of Pro12Ala polymorphism of peroxisome proliferator-activated receptor γ 2 gene on rosiglitazone response in type 2 diabetes," *Clinical Pharmacology & Therapeutics*, vol. 78, no. 2, pp. 202–208, 2005.
- [179] K.-H. Zhang, Q. Huang, X.-P. Dai et al., "Effects of the peroxisome proliferator activated receptor- γ coactivator-1 α (PGC-1 α) Thr394Thr and Gly482Ser polymorphisms on rosiglitazone response in Chinese patients with type 2 diabetes mellitus," *The Journal of Clinical Pharmacology*, vol. 50, no. 9, pp. 1022–1030, 2010.
- [180] H. Makino, I. Shimizu, S. Murao et al., "A pilot study suggests that the G/G genotype of resistin single nucleotide polymorphism at –420 may be an independent predictor of a reduction in fasting plasma glucose and insulin resistance by pioglitazone in type 2 diabetes," *Endocrine Journal*, vol. 56, no. 9, pp. 1049–1058, 2009.
- [181] H. Sun, Z.-C. Gong, J.-Y. Yin et al., "The association of adiponectin allele 45T/G and –11377C/G polymorphisms with type 2 diabetes and rosiglitazone response in Chinese patients," *British Journal of Clinical Pharmacology*, vol. 65, no. 6, pp. 917–926, 2008.
- [182] H.-L. Liu, Y.-G. Lin, J. Wu et al., "Impact of genetic polymorphisms of leptin and TNF- α on rosiglitazone response in Chinese patients with type 2 diabetes," *European Journal of Clinical Pharmacology*, vol. 64, no. 7, pp. 663–671, 2008.
- [183] J. Kirchheiner, S. Thomas, S. Bauer et al., "Pharmacokinetics and pharmacodynamics of rosiglitazone in relation to CYP2C8 genotype," *Clinical Pharmacology & Therapeutics*, vol. 80, no. 6, pp. 657–667, 2006.