Review Article

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

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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>
<thead>
<tr>
<th>Year</th>
<th>Locus</th>
<th>SNP</th>
<th>Chr.</th>
<th>Position</th>
<th>Allele (risk/other)</th>
<th>RAF*</th>
<th>OR</th>
<th>Probable mechanism</th>
<th>Candidate and large-scale association study</th>
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<th>RAF*</th>
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<th>Probable mechanism</th>
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* 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.

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<td>366,0197</td>
<td>T/C</td>
<td>0.317</td>
<td>1.1</td>
</tr>
<tr>
<td>2013</td>
<td>PAX4 [33]</td>
<td>rs10229583</td>
<td>7</td>
<td>127,034139</td>
<td>G/A</td>
<td>0.829</td>
<td>1.18</td>
</tr>
<tr>
<td>2013</td>
<td>MIR129-LEP [34]</td>
<td>rs791595</td>
<td>7</td>
<td>127,650,038</td>
<td>A/G</td>
<td>0.08</td>
<td>1.17</td>
</tr>
<tr>
<td>2013</td>
<td>SLC16A13 [34]</td>
<td>rs312457</td>
<td>17</td>
<td>688,1117</td>
<td>G/A</td>
<td>0.078</td>
<td>1.2</td>
</tr>
<tr>
<td>2013</td>
<td>GPSM1 [34]</td>
<td>rs11787792</td>
<td>9</td>
<td>138,371,969</td>
<td>A/G</td>
<td>0.874</td>
<td>1.15</td>
</tr>
</tbody>
</table>

* 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.

<table>
<thead>
<tr>
<th>Locus</th>
<th>SNP</th>
<th>Chr.</th>
<th>Position</th>
<th>Allele (risk/other)</th>
<th>RAF*</th>
<th>OR</th>
<th>Probable mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011 ST6GAL1</td>
<td>rs16861329</td>
<td>3</td>
<td>188149155</td>
<td>G/A</td>
<td>0.86</td>
<td>1.09</td>
<td>β-Cell function</td>
</tr>
<tr>
<td>2011 HNF4A</td>
<td>rs4812829</td>
<td>20</td>
<td>42422681</td>
<td>A/G</td>
<td>0.29</td>
<td>1.09</td>
<td>GWAS</td>
</tr>
<tr>
<td>2011 VPS26A</td>
<td>rs1802295</td>
<td>10</td>
<td>70601480</td>
<td>A/G</td>
<td>0.26</td>
<td>1.08</td>
<td>Unknown</td>
</tr>
<tr>
<td>2011 APOE3</td>
<td>rs2028299</td>
<td>15</td>
<td>88175261</td>
<td>C/A</td>
<td>0.31</td>
<td>1.1</td>
<td>Unknown</td>
</tr>
<tr>
<td>2011 HMG20A</td>
<td>rs7185752</td>
<td>15</td>
<td>75534245</td>
<td>G/A</td>
<td>0.52</td>
<td>1.09</td>
<td>Unknown</td>
</tr>
<tr>
<td>2011 GBR4</td>
<td>rs3923113</td>
<td>2</td>
<td>165210995</td>
<td>A/C</td>
<td>0.74</td>
<td>1.09</td>
<td>Insulin action</td>
</tr>
<tr>
<td>2013 TEMEM163</td>
<td>rs998451</td>
<td>2</td>
<td>135145758</td>
<td>G/A</td>
<td>1</td>
<td>1.56</td>
<td>β-Cell function</td>
</tr>
<tr>
<td>2013 SGGC</td>
<td>rs9552911</td>
<td>13</td>
<td>22762657</td>
<td>A/G</td>
<td>0.07</td>
<td>0.67</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

* 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.

During the past several decades, only a few loci conferring risk of T2D were identified through candidate gene approach with PPARγ Pro12Ala polymorphism being the first reported locus [8]. PPARγ is a transcription factor that plays a pivotal role in adipocyte differentiation. It was reported that PPARγ 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 HNFIB were also uncovered as established genes associated with T2D [11, 12]. WFS1 encodes wolframin, a membrane glycoprotein that maintains calcium homeostasis in 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]. HNFIB 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 (PPARγ, KCNJ11, TCF7L2, CDKAL1, CDKN2A/B, IGFBP2, HHEX/IDE, FTO, and SLC30A8) [13–18]. Except for PPARγ 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 1q, is a member of the homeobox family and encodes a transcription factor that may involve 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 × 10⁻⁸), with the loci being IAZF1, CDC123-CAMKID, TSPAN8-LGR5, THADA, ADAMTS9, and NOTCH2 [19]. Genetic variants in IAZF1, CDC123-CAMKID, 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 (IRSI), 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 × 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-β, P = 1.1 × 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...
\(\beta\)-cell functions, whereas the locus mapped in \textit{GCKR} shows a primary effect on insulin action [22]. In the same year, another genome-wide association study by Qi and colleagues identified 12 new signals with a combined \(P < 5 \times 10^{-8}\), including \textit{BCLI1A}, \textit{ZBED3}, \textit{KLF14}, \textit{TP53INP1}, \textit{TLE4}, \textit{CENTD2}, \textit{HMGA2}, \textit{HNF1A}, \textit{PRCI}, \textit{ZEBAN6}, \textit{DUSP9}, and \textit{KCNQ1} [24]. \textit{HNF1A} 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]. \textit{KCNQ1} 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]. \textit{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 \textit{BCARI}, \textit{MCAR}, \textit{CILP2}, \textit{ANKRD55}, \textit{TLEI}, \textit{KLHD5C5}, \textit{MGC21675}, \textit{ANKI}, \textit{ZMIZ1}, and \textit{GRB14} [25]. To assess the potential function of these loci, OGTT was employed to test insulin release and insulin sensitivity. \textit{ANKI} 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, \textit{GRB14} and \textit{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 T2D in East Asians.

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 \textit{KCNQ1} as a new susceptibility locus [70, 71]. \textit{KCNQ1} encodes the pore-forming \(\alpha\)-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, \textit{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 \textit{UBE2E2} and \textit{C2CD4A-C2CD4B}. Genetic variants in \textit{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 \textit{PTPRD} (protein tyrosine phosphatase receptor type D) and \textit{SRR} (serine racemase) [29]. \textit{PTPRD} is a protein tyrosine phosphatase and may play a role in the pathogenesis of T2D through increased insulin resistance [75]. \textit{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 \textit{GLIS3}, \textit{PEPD}, \textit{FITM2-R3HDML-HNF4A}, \textit{KCNK16}, \textit{MAEA}, \textit{GCCI-PAX4}, \textit{PSMD6}, and \textit{ZFAND} [30].

In 2012, another GWAS in Japanese populations revealed that rs515071 in \textit{ANKI} was associated with T2D at the genome-wide significance level [31]. \textit{ANKI}, 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, \textit{GRK5} and \textit{RASGRPI}, and the association signal for \textit{GRK5} seems to be specific to East Asians [32]. \textit{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 \textit{PAX4} was identified in a meta-analysis of three GWAS from Southern Han Chinese descendents [33]. As a member of the paired box family of transcription factors, \textit{PAX4} plays a critical role in pancreatic \(\beta\)-cell development and \(\beta\)-cell functions [80]. Further three new predisposing loci, \textit{MIRI29-LEP}, \textit{GPMI}, and \textit{SLC16A13}, with genome-wide significance for T2D were identified [34]. Rs791595 is located between \textit{MIRI29-1} and \textit{LEP}. The coding product of \textit{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 \textit{MIRI29} in diabetes remains unknown [81].

Besides these newly identified loci, some susceptible genes identified in Caucasians were also replicated in East Asians, such as \textit{PPARY}, \textit{KCNJ11}, \textit{TCF2}, \textit{TCF712}, \textit{CDKAL1}, \textit{CDKN2A-CDKN2B}, \textit{ID3-KIF11-HHEX}, \textit{IGF2BP2}, \textit{MTNR1B}, \textit{SLC30A8}, \textit{KCNQ1}, \textit{CDC123}, \textit{GLIS3}, \textit{HNFIB}, and \textit{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, KCNJI, TCF7L2, SLC30A8, HHEX, CDKN2A/B, IGF2BP2, CDKAL1, FTO, KCNQ1, JAZFI, 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 × 10−5 [109]. In consideration of the fact that all the above loci did not reach genome-wide significance (P < 5 × 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 × 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 KCNJI, TCF7L2, WFS1, HNF1B, IGF2BP2, CDKN2A-CDKN2B, CDKAL1, SLC30A8, HHEX, IDE, KCNQ1, THADA, TSPAN8/LGR5, CDC23/CAMKID, JAZFI, MTNRIB, DGKB/TMEM195, GCK, PROX1, ADCY5, SRR, CENTD2, ST6GAL1, HNF4A, KCNK16, FITM2-R3HDML-HNF4A, GLIS3, GRB14, ANKI, BARH1, RASGRF1, and TMEM163 may confer T2D risk through impaired β-cell function [16, 24, 44, 68, 111–114], whereas PPARγ, ADAMTS9, IRS1, GCKR, RBMS1/ITGB6, PTPRD, DUSP9, HMG2A, 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 SLC30A8 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 SLC30A8 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 the 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, IRS1, TCF7L2, NOS1AP, KCNQ1, CDKAL1, 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 sulfonylurea 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 SLCO1B1, SLC22A1, SLC47A1, SLC47A2, and ATM [159–167] were found to affect metformin efficacy. SLCO1B1 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, CYF3A4, IGF2BP2, SLC30A8, KCNQ1, KCNJ11, NAMPT, UCP2, MDRI, 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-1α, resistin, adiponectin, leptin, TNF-alpha, 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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