Diabetes in China: Epidemiology and Genetic Risk Factors and Their Clinical Utility in Personalized Medication

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The incidence of type 2 diabetes (T2D) has rapidly increased over recent decades, and T2D has become a leading public health challenge in China. Compared with European descents, Chinese patients with T2D are diagnosed at a relatively young age and low BMI. A better understanding of the factors contributing to the diabetes epidemic is crucial for determining future prevention and intervention programs. In addition to environmental factors, genetic factors contribute substantially to the development of T2D. To date, more than 100 susceptibility loci for T2D have been identified. Individually, most T2D genetic variants have a small effect size (10–20% increased risk for T2D per risk allele); however, a genetic risk score that combines multiple T2D loci could be used to predict the risk of T2D and to identify individuals who are at a high risk. Furthermore, individualized antidiabetes treatment should be a top priority to prevent complications and mortality. In this article, we review the epidemiological trends and recent progress in the understanding of T2D genetic etiology and further discuss personalized medicine involved in the treatment of T2D.

The increasing prevalence of type 2 diabetes (T2D) has become a global public health concern in the 21st century. Previously, T2D was mostly prevalent in affluent "Western" countries; however, currently, T2D occurs worldwide. According to the latest report in the International Diabetes Federation *Diabetes Atlas* (1), the overall prevalence of diabetes in adults is 9.1%, implying that 415 million adults suffer from diabetes globally. Moreover, 318 million adults have impaired glucose regulation and are at a high risk for developing diabetes in the future. China ranks number one, with the highest number of people with diabetes.

Environmental factors, including obesity, aging, diet, and physical activity; genetic factors; and epigenetic modification contribute to the accelerating diabetes epidemic. Knowledge of the risk factors that affect the incidence of T2D and the complications of T2D can advance the understanding of the pathophysiology of this disease and the development of effective preventive measures. Previously, numerous T2D susceptible loci have been successfully identified and replicated by genome-wide association studies (GWAS). Many scholars have attempted to develop a T2D risk model that includes the genetic risk factors that play a vital role in the prediction of T2D. Furthermore, a strategy to treat T2D is urgently needed. In addition to lifestyle interventions, conventional oral medications and insulin and personalized treatment based on pharmacogenomic, proteomic, and metabolomic approaches could help in choosing the appropriate therapy and thus improve the outcomes of patients with T2D.

This Perspective reviews the epidemiological trends and established risk factors of T2D in the Chinese population and discusses the clinical utility of genetic information in the prevention and personalized therapy of T2D.

EPIDEMIOLOGICAL TRENDS OF DIABETES IN CHINA

China, which is the most populous country, ranks number one with an estimate of 109.6 million adults with diabetes. Over the past three decades, the prevalence of diabetes in China has sharply increased. The prevalence of diabetes was reported to be less than 1% in 1980 (2), 5.5% in 2001 (3), 9.7% in 2008 (4), and 10.9% in 2013, according to the latest published nationwide survey (5) (Fig. 1). According to the 2013 survey, 4% of adults have been previously diagnosed

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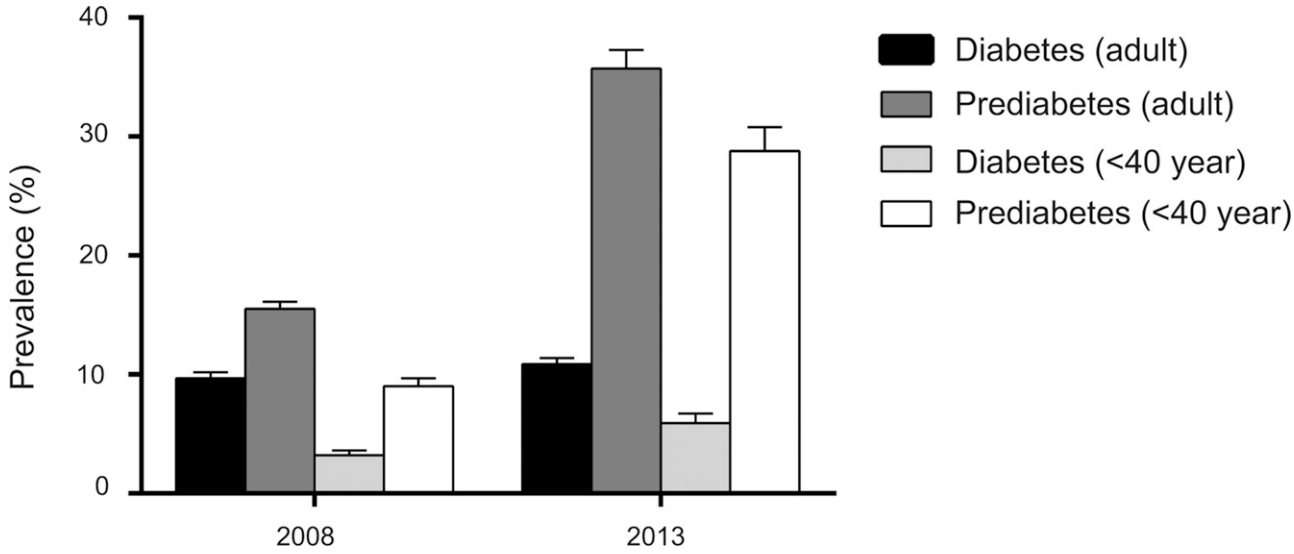

Figure 1—Prevalence of diabetes and prediabetes among Chinese adults or individuals <40 years of age, according to the 2008 and 2013 nationwide survey. Diabetes includes both previously diagnosed and previously undiagnosed diabetes. Prediabetes was defined as impaired fasting glucose or impaired glucose tolerance. I bars indicate 95% CIs.

with diabetes; 6.9% of patients have received a new diagnosis according to the American Diabetes Association 2010 criteria, which was 0.5% higher than that according to the World Health Organization 1997 criteria in which HbA_{1c} level ≥6.5% is not a criterion for the diagnosis of diabetes.

The prevalence of diabetes was higher in the senior population, men, urban residents, individuals living in economically developed areas, and overweight and obese individuals. The estimated prevalence of prediabetes in 2013 was 35.7%, which was much higher than the estimate of 15.5% in the 2008 survey. Similarly, the prevalence of prediabetes was higher in the senior population, men, and overweight and obese individuals. However, prediabetes was more prevalent in rural residents than in urban residents. As China is a multiethnic country, the 2013 survey also compared the prevalence of diabetes among different races. The crude prevalence of diabetes was 14.7% in the majority group, i.e., Chinese Han, which was higher than that in most minority ethnic groups, including Tibetan, Zhuang, Uyghur, and Muslim. The crude prevalence of prediabetes was also higher in the Chinese Han ethnic group. The Tibetan participants had the lowest prevalence of diabetes and prediabetes (4.3% and 31.3%). Notably, the prevalence of diabetes in the Manchu group was equal to that in the Chinese Han group, and the prevalence of prediabetes was even higher. However, this study did not include all minority ethnic groups in China.

In addition, the prevalence of diabetes in young people is relatively high and increasing. The prevalence of diabetes in the 20- to 39-year age-group was 3.2%, according to the 2008 national survey (4), and was 5.9%, according to the 2013 national survey (5). The prevalence of prediabetes also increased from 9.0% in 2008 to 28.8% in 2013 (Fig. 1). Young people suffering from diabetes have a higher risk of chronic complications, which are the major cause of mortality and morbidity in diabetes. According to a study conducted in Asia (6), patients with young-onset diabetes had higher mean concentrations of HbA_{1c} and LDL cholesterol and a higher prevalence of retinopathy (20% vs. 18%, P = 0.011) than those with late-onset diabetes. In the Chinese, patients with early-onset diabetes had a higher risk of nonfatal cardiovascular disease (7) than did patients with late-onset diabetes (odds ratio [OR] 1.91, 95% CI 1.81–2.02).

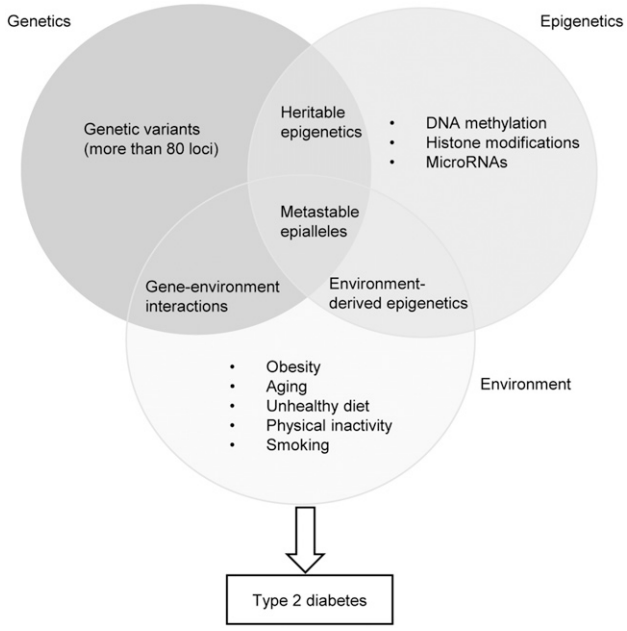

Figure 2—Role of genetics, epigenetics, and the environment in the development of T2D. The schematic diagram illustrates the independent and interacting effects of genetics, epigenetics, and the environment that can give rise to T2D risk.

Certainly, the diagnosis of T2D in China still faces challenges. First, both fasting plasma glucose and oral glucose tolerance tests require the patient to fast for at least 8 h, which decreases the opportunities for diagnosing diabetes. Second, as HbA_{1c} cutoff points vary according to ethnic groups, age, sex, and the prevalence of diabetes (8,9), the Chinese-specific diagnostic values for HbA_{1c} should be established. Bao et al. (10) proposed that an HbA_{1c} threshold of 6.3% was highly specific for detecting undiagnosed diabetes in Chinese. Nevertheless, China has a vast territory, therefore, a significant difference in availability and standardization of HbA_{1c} assay methods exists among laboratories, which limits the wide use of HbA_{1c} as a diagnostic tool.

RISK FACTORS FOR THE DIABETES EPIDEMIC IN CHINA

Environmental factors including obesity, aging, dietary pattern containing more refined food and fats, sedentary lifestyles, genetic factors, and epigenetic modifications all contribute to the accelerating diabetes epidemic in China (11) (Fig. 2).

Increasing Overall and Abdominal Obesity

As approximately 95% of patients with diabetes in China have T2D, the rapid increase in the prevalence of diabetes in China may be attributed to the increasing rates of overweight and obesity and the reduction in physical activity, which is driven by economic development, lifestyle changes, and diet (3,11). According to a series of nationwide surveys conducted by the China Physical Fitness Surveillance Center (12), the prevalence of overweight (BMI $\geq$23.0 to $<$27.5 kg/m^2) in Chinese adults aged 20–59 years increased from 37.4% in 2000 to 39.2% in 2005, 40.7% in 2010, and 41.2% in 2014, with an estimated increase of 0.27% per year. The prevalence of obesity (BMI $\geq$27.5 kg/m^2) increased from 8.6% in 2000 to 10.3% in 2005, 12.2% in 2010, and 12.9% in 2014, with an estimated increase of 0.32% per year (Fig. 3). The prevalence of central obesity increased from 13.9% in 2000 to 18.3% in 2005, 22.1% in 2010, and 24.9% in 2014, with an estimated increase of 0.78% per year. Notably, T2D develops at a considerably lower BMI in the Chinese population than that in European populations. According to the latest national survey, the prevalence of diabetes and prediabetes in participants with a BMI $<$23 kg/m^2 was 6.4% and 30.7%, respectively (5). The relatively high risk of diabetes at a lower BMI could be partially attributed to the tendency toward visceral adiposity in East Asian populations, including the Chinese population (13). Moreover, East Asian populations have been found to have a higher insulin sensitivity with a much lower insulin response than European descent and African populations, implying a lower compensatory β-cell function, which increases the risk of progressing to overt diabetes (14).

Genetic Factors

Known T2D Susceptible Loci

The etiology of T2D is known to have a considerable genetic component. According to estimates, the heritability of T2D ranges from 30 to 70% (15). According to the Framingham Offspring Study, the diabetes risk OR for an individual with one affected parent was 3.4–3.5, and the OR increased to 6.1 when both parents were affected (16). Twin studies have also revealed that the concordance rate was higher in monozygotic twins (0.29–1.00) than in dizygotic twins (0.10–0.43), indicating a significant genetic basis for T2D (17). Furthermore, there is a significant difference in the prevalence of

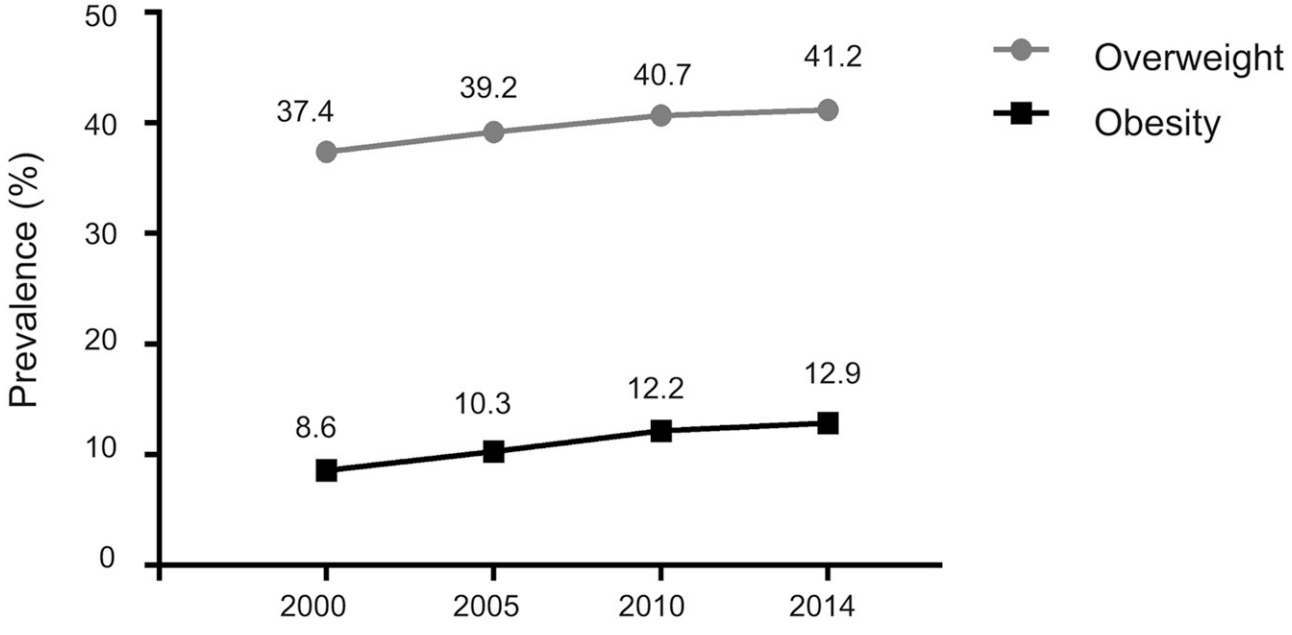

Figure 3—Secular trends in overweight and obesity (in adults aged 20–59 years) associated with the increasing prevalence of diabetes in China, according to a serious of nationwide surveys. Adult overweight was defined according to World Health Organization definition for Asians, with BMI $\geq$23.0 to $<$27.5 kg/m^2. Adult obesity was defined according to World Health Organization definition for Asians, with BMI $\geq$27.5 kg/m^2.

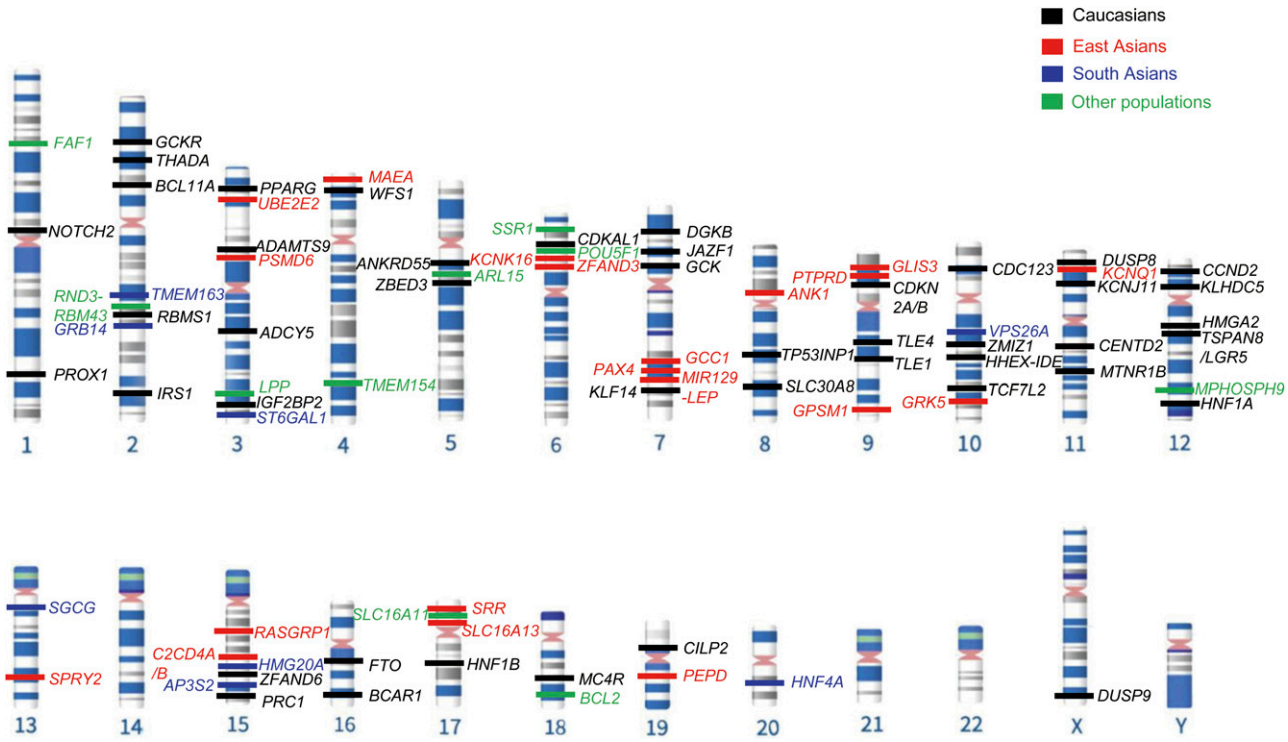

Figure 4—Summary of diabetes susceptibility loci among major ancestry groups. Indicated are the populations in which the loci were initially detected: Caucasians (European descendants), East Asians, South Asians, and other populations.

T2D among different ethnic groups. European and Asian populations are mildly and moderately susceptible to T2D, respectively. However, Pima Indians have a very high prevalence of T2D, and approximately 50% of adults above 35 years of age having T2D.

Over the past two decades, linkage analyses, candidate gene approaches, and large-scale GWAS have successfully identified more than 100 genes that confer susceptibility to T2D among the world's major ethnic populations (see Fig. 4 for a summary of common T2D loci), most of which were discovered in European populations. However, less than 50% of these European-derived loci have been successfully confirmed in East Asian populations. The studies in Chinese (18,19) investigating these variants discovered in the European populations in the Han Chinese population found that only the variants near *PPARG*, *KCNJ11*, *CDKAL1*, *CDKN2A/B*, *IDE-KIF11-HHEX*, *IGF2BP2*, *SLC30A8*, *HNF1B*, *DUSP9*, *ZFAND3*, *FTO*, and *TCF7L2* were associated with T2D. The failure of the replication study may be due to discrepancies in the allelic frequencies and effect sizes in different ethnic groups. Therefore, there is a need to identify specific genes that are associated with T2D in other ethnic populations.

In 2008, the first GWAS of T2D in East Asian populations were concurrently conducted by two independent Japanese groups and confirmed that *KCNQ1*, which was previously implicated in insulin secretion, was a novel T2D susceptibility locus with the OR ranging from 1.26 to 1.41 (20,21). *KCNQ1* encodes the pore-forming α-subunit of the voltage-gated K^+ channel, which is mainly expressed in the cardiac muscles and pancreas. The association between *KCNQ1* and T2D was further confirmed in Korean (22), Chinese (23), and Singaporean (24) populations. Therefore, *KCNQ1* is considered the strongest locus for T2D in populations of East Asian ethic origin. Subsequently, additional GWAS have been performed in East Asian populations. In 2010, five new loci, namely, *PTPRD*, *SRR*, *SPRY2*, *UBE2E2*, and *C2CD4A/B*, were demonstrated to confer T2D risk in East Asian populations (25–27). In 2012, Cho et al. (28) performed a meta-analysis of three-stage GWAS in East Asian populations and identified eight novel T2D-associated loci. These loci were mapped in or near *GLIS3*, *PEPD*, *FITM2-R3HDML-HNF4A*, *KCNK16*, *MAEA*, *GCC1-PAX4*, *PSMD6*, and *ZFAND3* and increased the T2D risk by 8–13%. Subsequently, three new T2D loci were discovered in Han Chinese populations as susceptible loci for T2D in 2013, namely, *PAX4* (29), *GRK5* (30) and *RASGRP1* (30). Notably, the rs10229583 variant, which is located at 7q32 near *PAX4* and plays a critical role in the development of pancreatic β-cells, could increase the T2D risk by 18%.

Although many genetic loci have been shown to confer susceptibility to T2D, the mechanism by which these loci participate in the pathogenesis of T2D remains unknown. Most T2D loci are located near genes that are related to β-cell function, including *TCF7L2*, *WFS1*, *KCNJ11*, *HNF1B*, *IGF2BP2*, *CDKN2A/B*, *SLC30A8*, *HHEX/IDE*, *CDKAL1*, *KCNQ1*, *THADA*, *TSPAN8/LGR5*, *CDC123/CAMK1D*, *JAZF1*, *MTNR1B*, *GCK*, *PROX1*, *DGKB/TMEM195*, *ADCY5*, *CENTD2*, *SRR*, *ST6GAL1*, *KCNK16*, *HNF4A*, *FITM2-R3HDML-HNF4A*, *GLIS3*, *ANK1*,

BCAR1, *GRB14*, *RASGRP1*, and *TMEM163*, whereas *PPARG*, *ADAMTS9*, *GCKR*, *IRS1*, *PTPRD*, *DUSP9*, *RBMS1/ITGB6*, *HMGA2*, *KLF14*, *GRB14*, *ANKRD55*, and *GRK5* have an impact on the action of insulin, emphasizing the important role of β-cell dysfunction in the pathogenesis of T2D.

In addition, most single nucleotide polymorphisms (SNPs) contributing to the T2D risk are located in introns, but whether these SNPs directly modify gene expression or are involved in linkage disequilibrium with unknown causal variants remains to be investigated. Furthermore, the loci discovered thus far collectively account for less than 15% of the overall estimated genetic heritability. More studies, including trans-ethnic mapping, and the use of new technologies, such as deep sequencing and whole-exome sequencing, are needed to further identify the underlying genetic factors of T2D in Chinese and other populations.

Clinical Utility of Genetic Information: Prediction of T2D

The early identification of individuals at a high risk of T2D can prevent or delay the onset of T2D through effective lifestyle and pharmacological interventions. Models based solely on conventional risk factors have achieved only a moderate predictive performance (31). Therefore, T2D risk models incorporating genetic information are needed to increase the predictive performance.

Numerous studies have constructed a genetic risk score (GRS) to evaluate the predictive ability of current genetic information. The GRS combines information from multiple variants to represent an individual's genetic predisposition to T2D. Between 2006 and 2016, 38 studies were performed to construct a GRS model and evaluate the performance of the GRS model in predicting the prevalence or incidence of T2D. Of these studies, 17 were case-control or cross-sectional studies, 18 were prospective cohort studies, 2 were nested case-control studies, and 1 was a mixed cohort and case-control study.

Case-Control and Cross-Sectional Studies. Studies exploring the performance of T2D genetic risk models were first conducted in European populations. These studies incorporated 3–38 SNPs and reported that each additional risk allele was associated with a 7–28% increased risk of T2D. In 2009, Hu et al. (19) first constructed a GRS model using 11 SNPs and assessed the predictive effect of this model in a Chinese population (1,523 control vs. 1,359 case subjects). The results showed that the OR for T2D per risk allele was 1.265 (95% CI 1.214–1.318). Similarly, Imamura et al. (32) investigated a GRS model combining 49 SNPs in a Japanese population (1,786 control vs. 2,613 case subjects) and found that individuals with a GRS $\geq$60 were approximately 10-fold more likely to develop T2D than those with a GRS $<$46. Thus, a GRS model combining multiple coexisting genetic variants may be useful for identifying individuals at high genetic risk for developing T2D.

Prospective Studies. Genetic risk models have also been useful in predicting incident T2D in prospective studies. In 2013, Andersson et al. (33) genotyped 46 variants and subsequently constructed a GRS model in a Danish population (n = 5,850 at baseline). The risk of incident T2D was increased with a hazard ratio (HR) of 1.06 (95% CI 1.03–1.08) per risk allele during a median follow-up of 11 years. In 2014, another study used 65 and 89 SNPs to construct two GRS models (GRS-1, 65 European-derived loci associated with T2D; GRS-2, GRS-1 combined with 24 fasting plasma glucose–raising SNPs) and explored the contribution of the GRS to the incidence of T2D in 4,075 individuals in the Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) study over a 9-year follow-up period (34). The two GRS models were both significantly associated with an increased incidence of T2D (per allele: GRS-1, HR 1.07, 95% CI 1.03–1.10; GRS-2, HR 1.05, 95% CI 1.02–1.08).

However, few studies focusing on the capacity of the GRS to predict the incidence of T2D in East Asian populations have been conducted. In 2013, Kwak et al. (35) constructed a weighted GRS (wGRS) model based on 48 T2D genetic variants in a prospective cohort study involving 395 Korean women with gestational diabetes mellitus. After a median follow-up period of 3.8 years, the women with gestational diabetes mellitus who developed diabetes had a significantly higher wGRS than those who did not develop diabetes (9.36 $\pm$ 0.92 vs. 8.78 $\pm$ 1.07, $P < 1.56 \times 10^{-7}$). Recently, one study (36) genotyped 89 SNPs to determine T2D susceptibility in a Chinese cross-sectional population (n = 6,822) and then selected 40 SNPs that were significantly associated with the diabetes risk ($P < 0.05$) to construct a wGRS. These authors found that the wGRS could predict the incidence of T2D and impaired glucose regulation in the Cox model (HR 1.129, 95% CI 1.026–1.242) in a Chinese 9-year prospective cohort study (n = 2,495). Moreover, the wGRS predicted blood glucose deterioration due to the changes in function of β-cells (β -0.0480, $P = 9.66 \times 10^{-5}$ and β -0.0303, $P = 3.32 \times 10^{-5}$ for Stumvoll first- and second-phase insulin secretion, respectively).

Predictive Performance of Genetic Variants Compared With Conventional Clinical Risk Models

The areas under the receiver operating characteristic curves (AUCs) are usually used to assess the discriminative accuracy of an approach. The AUC values range from 0.5 to 1.0, where an AUC of 0.5 represents a lack of discrimination and an AUC of 1 represents perfect discrimination. An AUC $\geq$0.75 is considered clinically useful. The dominant conventional risk factors, including age, sex, BMI, waist circumference, blood pressure, family history of diabetes, physical activity level, smoking status, and alcohol consumption, can be combined to construct conventional risk factor–based models (CRM). Several studies have compared the predictive capacities of models with and without genetic information. The addition of genetic markers to a CRM could slightly improve the predictive performance. For example, one European study showed that the addition of an 11-SNP GRS to a CRM marginally improved the risk prediction (AUC was 0.74 without and 0.75 with the genetic markers, $P < 0.001$) in a prospective cohort of 16,000 individuals

(37). A meta-analysis (38) consisting of 23 studies investigating the predictive performance of T2D risk models also reported that the AUCs only slightly increased with the addition of genetic information to the CRM (median AUC was increased from 0.78 to 0.79).

The potential explanation for this phenomenon is that genetic variants may have exerted their effect on the onset of T2D through certain conventional risk factors (39). For example, a family history of T2D, which is a major risk factor included in most CRMs, could capture the genetic information provided by the GRS (39). Moreover, gene–gene and gene–environment interactions also contribute to the diabetes epidemic and should be considered to assess the enhanced predictive capacity of genetic variants.

Emerging Risk Factors From Early Life

An increasing number of studies have highlighted that early nutrition has a persistent effect on the risk of diabetes in later life (40,41). China's Great Famine of 1959–1962 is considered to be the largest and most severe famine of the 20th century (42), resulting in an estimated mortality of 30 million. Li et al. (43) found that offspring of mothers exposed to the Chinese famine have a 3.9-fold increased risk of diabetes or hyperglycemia as adults. A more recent study (the Survey on Prevalence in East China for Metabolic Diseases and Risk Factors [SPECT-China]) conducted in 2014, among 6,897 adults from Shanghai, Jiangxi, and Zhejiang provinces, had the same conclusion that famine exposure during the fetal period (OR 1.53, 95% CI 1.09–2.14) and childhood (OR 1.82, 95% CI 1.21–2.73) was associated with diabetes (44). These findings indicate that undernutrition during early life increases the risk of hyperglycemia in adulthood and this association is markedly exaggerated when facing overnutrition in later life. In addition, exposure to maternal overnutrition, obesity, or diabetes during pregnancy also predisposes the offspring to develop diabetes (45). Studies in the Pima Indian population were among the first to show a high risk of diabetes and obesity among children born to mothers with diabetes (46). Among Chinese adults and adolescents from the community, it was found that a maternal history of diabetes was associated with 59% and 88% increased risk of obesity and central obesity, respectively, as well as more insulin resistance and β-cell function impairment (47), highlighting potential intergenerational effects.

The potential mechanism underlying the observed links between early life exposures and later risk of metabolic diseases, such as diabetes, is considered to be epigenetic regulation. DNA methylation is the most well studied, and the differential methylation of gene clusters that regulate metabolism, insulin signaling, and nutrient sensing has been reported to be associated with maternal undernutrition or maternal overnutrition and maternal diabetes (48,49). For instance, individuals exposed to famine prenatally had reduced DNA methylation in the imprinted IGF2 locus, compared with their unexposed, same-sex siblings (50). Therefore, it appears that epigenetic mechanisms are very significant in the maternal-placental-fetal transmission of metabolic phenotypes.

Other Risk Factors

Several other common diseases have also been linked to diabetes risk in the Chinese population. Hypertriglyceridemia, one major type of dyslipidemia, has been demonstrated to be associated with increased diabetes risk (51). Moreover, about 15% of general population in China has nonalcoholic fatty liver disease, which is a strong predictor of T2D (52). In a recent meta-analysis involving 20 studies, nonalcoholic fatty liver disease significantly increased twofold risk of incident T2D and metabolic syndrome during 5-year follow-up (53). However, this relationship is bidirectional, as T2D substantially predicts the development of these metabolic disorders. According to the 2007–2008 China National Diabetes and Metabolic Disorders Study, the risk of cardiovascular disease in patients with diabetes was 3.6 times higher than that of the normal population (54).

THERAPEUTIC PERSPECTIVE

Current T2D Therapy in China

Although there are various treatment patterns for diabetes, the current control of T2D in China is not optimistic. According to the survey of China noncommunicable chronic diseases, the proportion of diabetes treatment was 41.8% in urban residents, as opposed to 27.6% in rural residents. A recent study indicated that only half of patients who receive treatment had adequate glycemic control (55). In addition, achieving adequate control of risk factors for cardiovascular disease in patients with T2D also remains a clinical challenge. The "3B Study," which was a cross-sectional, multicenter observational study in China, aimed to investigate the blood glucose, blood pressure, and blood lipid (3Bs) control among patients with T2D (56). The proportion of patients who achieved their individual target goals for the control of blood glucose (HbA_{1c} <7%), blood pressure (systolic blood pressure <130 mmHg, diastolic blood pressure <80 mmHg), and blood lipids (total cholesterol <4.5 mmol/L) accounted for 47.7%, 28.4%, and 36.1%, respectively. Additionally, only 5.6% of patients achieved all three target goals. Thus, the development of appropriate therapies is needed to achieve normoglycemic levels and prevent diabetes-related morbidity and mortality in Chinese patients with T2D.

The pathogenetic mechanisms of diabetes in the Chinese population are associated with a more serious defect in insulin secretion, leading to the unique clinical characteristics of higher postprandial blood glucose levels. Specific treatment guidelines suitable for the Chinese population should be established instead of using guidelines from Western countries. According to the Chinese guidelines for T2D by the Chinese Diabetes Society, lifestyle interventions, including diet and exercise, are fundamental for the treatment of diabetes, and these interventions should be sustained throughout the clinical course. Pharmacological treatment is applied if lifestyle interventions cannot help patients achieve their individual target goals of blood glucose control. Oral medications, insulin, and insulin analogs are used for the treatment of T2D. The first-line oral antidiabetes agent for

patients with T2D is metformin, which downregulates gluconeogenesis in the liver. Due to the characteristics of postprandial hyperglycemia in Chinese patients, an α-glucosidase inhibitor or insulin secretagogue is recommended instead of metformin for newly diagnosed patients who experience gastrointestinal side effects. If metformin monotherapy treatment fails to control glycemia, secondary oral medications, including sulfonylureas, glinides, thiazolidinediones, and dipeptidyl peptidase 4 inhibitors, should be used. Glucose-like peptide 1 analogs are the third oral medication option according to this guideline. Insulin and insulin analogs are recommended for glycemia control in newly diagnosed patients with oral medication application failure, severe pancreatic islet β-cell dysfunction, long-term poorly controlled blood glucose, or various acute or chronic complications.

Future Personalized Medicine for the Treatment of Diabetes

In diabetes, precedent for the successful application of pharmacogenetic concepts exists in its monogenic subtypes, such as maturity-onset diabetes of the young (MODY). Individual patients with HNF-4α/MODY1 and HNF-1α/MODY3 mutations have been reported as being sensitive to the hypoglycemic effects of sulfonylurea therapy (57,58). One randomized crossover trial showed that patients with MODY3 had a 5.2-fold greater response to sulfonylurea gliclazide than to biguanide metformin and 3.9-fold greater response to gliclazide than those with T2D (59). The mechanism of sulfonylureas that could treat MODY1 and MODY3 effectively is demonstrated to act on K_{ATP} channel, downstream of β-cell defect (60). Recently, pharmacogenomics of T2D has also been developed.

Pharmacogenomics of T2D

Clinically, patients who receive similar antidiabetes regimens demonstrate large variability in drug disposition, glycemic response, tolerability, and incidence of adverse effects. This discrepancy may be due to biological and nonbiological factors. Psychological and social factors are crucial nonbiological factors. Biological factors include genetic and nongenetic factors that are involved in pharmacokinetics (drug absorption, distribution, metabolism, and excretion) and pharmacodynamics (drug targets, drug mechanism of action and reaction). Age; sex; gastrointestinal, liver, and kidney functions; and drug interactions are nongenetic factors. The genetic factors include polymorphisms in genes encoding molecules that are involved in drug metabolism, such as enzymes, transporters, receptors, and signal transduction pathways, that result in drug pharmacokinetics and pharmacodynamics differences, leading to different curative effects and adverse reactions in patients under the same treatment.

Pharmacogenomics mainly focus on the genetic polymorphisms that play a key role in the pharmacokinetic and pharmacodynamic differences, eventually guiding individualized treatment and helping in choosing the appropriate types of drugs to avoid adverse drug reactions and improve the safety of the drug treatment. Various studies have investigated the genetic markers that are involved in pharmacokinetics. Variations in the cytochrome P450 (CYP) enzymes contribute to oral antidiabetes drug metabolism in the liver and affect drug disposition and efficacy. Genetic variants in *CYP2C9*2* (I359L) and *CYP2C9*3* (R114C) were associated with a lower blood sulfonylurea clearance (61,62). Furthermore, variants in *CYP2C8* were found to influence the efficacy of repaglinide and rosiglitazone (63). However, the researchers failed to find an association between three polymorphisms, i.e., *CYP2C8*3*, *CYP3A4*18*, and *CYP2C9*3*, and the therapeutic efficacy of repaglinide or rosiglitazone in newly diagnosed Chinese T2D patients. Furthermore, genetic polymorphisms in drug transporters have become a hot research topic worldwide. Various studies have shown that rs12208357, rs34130495, rs34059508, and rs72552763 are related to the *SLC22A1* gene, which encodes organic cation transporter 1, and are genetic markers for metformin efficacy and excretion (64–67). In addition, polymorphisms in the *SLCO1B1* gene, which encodes organic anion transporting polypeptide 1B1, play a key role in the therapeutic effects of repaglinide and rosiglitazone (68,69). However, genetic variants responsible for the pharmacodynamics of antidiabetes agents have been less frequently studied. Two polymorphisms, i.e., *KCNJ11* and *ABCC8*, which encode two types of K_{ATP} channel subunits in pancreatic β-cells, were correlated with the efficacy of sulfonylurea (70). Moreover, investigations of T2D susceptibility genes have been focused on whether these genes are associated with the efficacy of hypoglycemic agents to a certain extent. The SNP rs11212617, which is located near the *ATM* locus, was found to be associated with the HbA_{1c} levels in response to metformin in a large-scale GWAS conducted in European T2D populations (71). One study has demonstrated that the *PAX4* variants rs6367136 and rs10229583 and the *PSMD6* variant rs831571 were correlated with the therapeutic efficacy of repaglinide and rosiglitazone in Chinese T2D patients (72,73).

Proteomics and Metabolomics of T2D

In addition to genetic markers, proteomic and metabolomic methods have been widely used to shed light on the basic pathophysiology of T2D and identify available molecular markers for personalized medicine. Personalizing treatment based on pharmacogenomic, proteomic, and metabolomic approaches can helpful in choosing the appropriate therapy, improve the outcomes of many T2D patients by reducing the chances of therapy failures and complications, and identify the at-risk relatives and family members of patients with diabetes. However, prior to the clinical implementation of personalized medicine, individualized diabetes management must be developed by combining genetic diagnosis with biomarker identifications. First, because the function of a single genetic marker is limited, a general genetic model combining the joint effects of multiple loci should be established to predict the efficacy of oral antidiabetes drugs. Second, because T2D comprises a group of complex disorders, there are many challenges in selecting among the drug

treatment options, and the number of clinical trials using an adequate design and power to translate genetic findings into clinical practice is limited. Third, researchers and pharmaceutical companies should place more focus on diversity, localization, and affordably priced biochips for diabetes diagnosis and detection prior to the application of personalized medicine. Therefore, a better understanding of the genetic and nongenetic factors is crucial for developing appropriate pharmaceutical intervention programs that can guide clinical individualized treatment.

SUMMARY

T2D can no longer be considered a disease of affluent nations because more than 60% of the world's population with diabetes comes from developing countries. China is a major epicenter in the diabetes epidemic. The increase in the prevalence of T2D is linked to changes in lifestyle, the increased prevalence of obesity, and genetic factors. Despite great advances in genetic studies, the clinical utility of genetic information in the prediction, early identification, and prevention of T2D remains in its preliminary stage. Pharmacogenomics is an emerging field that explores the role of inherited and acquired genetic variants in drug response and efficacy and thus can make contributions to antidiabetes drug selection. As the loci identified thus far explain only a small amount of the estimated heritability of T2D, intensive studies should be conducted to further identify T2D causal variants, epigenetic modifications, gene–gene interactions, and gene–environment interactions and to translate novel findings to clinical applications.

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