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Genetics of Type 2 Diabetes in European Populations

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Abstract

Type 2 diabetes (T2D) has become a leading health problem throughout the world. It is caused by both environmental and genetic factors and interactions between them. However, until very recently, the T2D susceptibility genes have been poorly understood. During the past 5 years, with the advent of genome-wide association studies (GWAS), a total of 58 T2D susceptibility loci have been associated with T2D risk at a genome-wide significance level ($P < 5 \times 10^{-8}$) and evidence shows that most of these genetic variants influence pancreatic β -cell function. Most novel T2D susceptibility loci were identified through GWAS in European populations and later confirmed in other ethnic groups. Although the recent discovery of novel T2D susceptibility loci has contributed substantially to our understanding of the pathophysiology of the disease, clinical utility of these loci in disease prediction and prognosis is limited. More studies using multiethnic meta-analysis, gene-environment interaction analysis, sequencing analysis, epigenetic analysis, and functional experiments are needed to identify new susceptibility T2D loci and causal variants and to establish biological mechanisms.

Keywords

Europeans; Genetics; Genome-wide association studies; Type 2 diabetes

Introduction

Type 2 diabetes (T2D) has become a leading health problem throughout the world, not only in Western countries, but also in developing countries. According to the International Diabetes Federation, the total number of people with diabetes is projected to rise from current estimates of 366 million to 552 million by the year 2030, with two-thirds of all diabetes cases occurring in low- to middle-income countries.¹ In addition to lifestyle factors, there is compelling evidence that T2D has a strong genetic component. The concordance of T2D in monozygotic twins (~70%) is much higher compared to dizygotic twins (20–30%).² A family history confers first-degree relatives a 3-fold increase risk of developing T2D.³ It has also been suggested that ethnic differences in the prevalence of T2D could be ascribed to genetic differences.⁴ Classic genetic research conducted with twins and with biological and adoptive families, consistently supports genetic links to T2D. However, until very recently, T2D susceptibility genes have been poorly understood. With the recent advent of genome-wide association studies (GWAS), a number of T2D susceptibility loci have been

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identified during the past 5 years. The purpose of the present review is to summarize the research on recently established T2D susceptibility genes in European populations. The review will also briefly discuss the potential mechanisms, risk prediction, and gene-environment interactions underlying T2D.

Detection and validation of T2D susceptibility loci

With rapid improvements in high-throughput SNP genotyping technology and the development of the HapMap project, the identification of T2D susceptibility genes has changed dramatically. Since the identification of *PPARG* and *KCNJ11* through candidate gene studies and *TCF7L2* through large-scale association analysis, the emergence of GWA studies has dramatically increased the number of validated T2D susceptibility genes. To date, a total of 58 loci have been established to be associated with T2D at a genome-wide significance level ($P < 5 \times 10^{-8}$). Among them, 39 loci were identified in European populations (Table 1), and the other 19 loci were identified in Asian populations (Please see the complementary review article by Jia et al. for details regarding genetics of T2D in Asian populations).

Candidate gene studies

During the past 2 decades, only four T2D susceptibility loci were identified through the candidate gene approach. Though the loci were ultimately validated, numerous candidate genetic association analyses for T2D were carried out, but failed to be replicated. The Pro12Ala polymorphism (rs1801282) in *PPARG* and E23K (rs5219) polymorphism in *KCNJ11* were the first robustly replicated signals associated with T2D. *PPARG* encodes the nuclear receptor PPAR- γ which is predominantly expressed in adipose tissue where it regulates the transcription of genes involved in adipogenesis. It is also a molecular target for thiazolidinedione compounds, a class of insulin-sensitizing drugs used to treat T2D. A non-synonymous SNP changing a proline in position 12 protein to alanine, Pro12Ala, was shown to be associated with increased insulin sensitivity and protection against T2D.⁵ A meta-analysis⁶ that strongly supported the association between the Pro12Ala variant and T2D was also confirmed by recent GWAS.⁷⁻⁹ *KCNJ11* encodes KIR6.2, a subunit with receptor 1 (SUR1) (encoded by *ABCC8*), and forms an ATP-sensitive potassium channel. The ATP-sensitive potassium channel regulates glucose-dependent insulin secretion in pancreatic beta-cells and it is also a molecular target for a class of diabetes drug, the sulfonylureas. A Glu23Lys polymorphism (E23K) gene has been associated with T2D in candidate gene studies^{10, 11} and was also confirmed in GWAS.⁷⁻⁹

More recently, the associations between genetic variants in *WFS1* and *HNF1B* were identified from in-depth studies of candidate genes. *WFS1* encodes wolframin, a membrane glycoprotein that maintains calcium homeostasis of the endoplasmic reticulum. Mutations in this gene may cause Wolfram syndrome which is characterized by diabetes insipidus, juvenile-onset non-autoimmune diabetes mellitus, optic atrophy, and deafness.¹² In a study of 1,536 SNPs in 84 candidate genes involved in pancreatic beta cell function and survival, only *WFS1* was associated with T2D.¹³ The association between the lead SNP rs10010131 and T2D was confirmed in a large meta-analysis.¹⁴ *HNF1B*, also known as *TCF72*, encodes hepatocyte nuclear factor 1 homeobox B (transcription factor 2), a liver-specific factor of the homeobox-containing basic helix-turn-helix family. Mutations in the *HNF1B* gene have been identified as the cause of maturity onset diabetes of the young type 5 (MODY5).¹⁵ Association between *HNF1B* genetic variants and T2D was first reported in a candidate genetic association study tested for known MODY genes.¹⁶ A GWAS initially designed for prostate cancer confirmed *HNF1B* as a T2D susceptibility gene.¹⁷

Large-scale association analysis

TCF7L2 is the first T2D susceptibility gene identified by large-scale association analysis,¹⁸ a ‘hypothesis-free’ association approach. The strong association between common variants in *TCF7L* and risk of T2D was highly confirmed in numerous replication studies and GWAS,^{7–9} with a per-allele odds ratio of ~1.4. *TCF7L2* encodes a transcription factor that is a crucial component of the Wnt signaling pathway and that had not been considered as a candidate for type 2 diabetes. Current evidence indicates that *TCF7L2* may confer type 2 diabetes risk through impaired beta-cell function and insulin secretion, incretin effects, and dysregulation of proglucagon gene expression.^{19, 20}

Very recently, a large-scale meta-analysis of 39 studies by using a custom ~50,000 SNP genotyping array with ~2000 candidate genes identified two additional type 2 diabetes loci at genome-wide significance, *GATAD2A* and *BCL2*.²¹ *GATAD2A* encodes the GATA zinc finger domain containing 2A, a transcriptional repressor that interacts with the methyl-CpG-binding domain proteins MBD2 and MBD3. Methyl-CpG-binding domain proteins are involved in functional responses of methylated DNA. The lead SNP rs3794991 in *GATAD2A* is in strong LD ($r^2 > 0.90$ in HapMap CEU) with another SNP rs16996148, previously identified to be associated with low-density lipoprotein cholesterol and triglycerides levels in GWAS.²² *BCL2* encodes an integral outer mitochondrial membrane protein that plays an anti-apoptotic role but has not previously been implicated in T2D.

Genome-wide association studies in European populations

During the past 5 years, GWAS have made the most important contributions to identifying novel T2D susceptibility loci. In 2007, the first wave of T2D GWAS carried out in European populations identified 6 novel susceptibility loci: *SLC30A8*, *HHEX/IDE*, *CDKAL1*, *CDKN2A/B*, *IGF2BP2*, and *FTO*.^{7–9, 23–25} Subsequent studies have shown that diabetes-risk alleles in these 5 loci were associated with reduced insulin secretion,^{26–29} while *FTO*, the first and strongest obesity gene identified so far,^{30, 31} may confer T2D risk through its primary effect on adiposity.^{8, 9, 30, 31}

In 2008, a meta-analysis of three GWAS (Diabetes, Genetics, Replication and Meta-analysis, DIAGRAM Consortium) identified 6 additional T2D susceptibility loci: *NOTCH2*, *THADA*, *ADAMTS9*, *JAZF1*, *CDC123/CAMK1D*, and *TSPAN8/LGR5*.³² Genetic variants in *JAZF1*, *CDC123/CAMK1D*, *TSPAN8/LGR5*, *THADA*, and *ADAMTS9* have been shown to be associated with impaired glucose-stimulated insulin secretion in subsequent studies.^{33, 34}

In 2009, only one novel loci, *IRS1*, was identified by GWAS for T2D,³⁵ but three groups concurrently reported another new T2D loci, *MTNR1B*, in follow-up analysis of GWAS for fasting glucose.^{36–38} *IRS1* encodes insulin receptor substrate 1 that is phosphorylated by insulin receptor tyrosine kinase and is essential to insulin signaling pathway. The risk allele of the rs2943641 in *IRS1* was also found to be associated with insulin resistance and hyperinsulinemia in human populations, and was associated with reduced basal levels of IRS1 protein and decreased phosphatidylinositol-3 kinase activity in skeletal muscles.³⁵ *MTNR1B* encodes melatonin receptor 1B, one of two known human melatonin receptors. Melatonin is a neurohormone and was reported to influence insulin secretion and glucose levels in previous studies.^{39–41}

The most recent efforts in identifying T2D susceptibility loci have been made by collaborative meta-analyses of individual GWAS data. In early 2010, by combining the data from 21 GWAS, the Meta-analysis of Glucose and Insulin-related traits Consortium (MAGIC) identified 18 loci associated with fasting glucose and/or fasting insulin, and five

of these loci were demonstrated as T2D susceptibility loci: *ADCY5*, *PROX1*, *GCK*, *GCKR*, and *DGKB-TMEM195*.⁴² A GWAS conducted in the Nurses' Health Study (NHS) and Health Professional Follow-up Study (HPFS) in combination with validation data from 11 independent GWAS, identified a new T2D susceptibility locus, *RBMS1*, on chromosome 2q24.⁴³ Genetic variants in this region were nominally associated with fasting glucose and HOMA-IR in the MAGIC consortium. The updated meta-analysis conducted in the DIAGRAM consortium increased the discovery sample size which substantially expanded the number of T2D susceptibility loci (Figure 1),⁴⁴ and 12 new loci were identified: *BCL11A*, *ZBED3*, *KLF14*, *TP53INP1*, *TLE4*, *CENTD2*, *HMGA2*, *HNF1A*, *PRC1*, *ZFAND6*, *DUSP9*, and *KCNQ1* (a second independent signal in this locus which was first identified in East Asian GWAS^{45, 46}). Of these recently identified loci, few could have been considered strong biological candidates prior to these studies. *GCK* encodes glucokinase which is the key glucose phosphorylation enzyme responsible for the first rate-limiting step in the glycolysis pathway and which regulates glucose-stimulated insulin secretion from pancreatic beta cells and glucose metabolism in the liver; and *GCKR* encodes glucokinase regulator. Both genes have previously been considered as candidates, but the associations with T2D were not strong in earlier studies.^{7, 47–49} *HNF1A* encoding hepatocyte nuclear factor 1, together with *HNF2B* and *HNF4A*, have been known as MODY genes.¹⁵ *DUSP9* is the first reported signal at the X-chromosome, and it encodes dual specificity phosphatase 9, a mitogen-activated protein kinase that has a potential role in the regulation of insulin action in mice.⁵⁰

Biological mechanisms of T2D susceptibility loci

T2D is characterized by insulin resistance and impaired β -cell function. To date, identified T2D susceptibility loci appear to influence β -cell function rather than insulin resistance (Table 1). Numerous studies have suggested that genetic variants in or near *KCNJ11*, *TCF7L2*, *WFS1*, *IGF2BP2*, *CDKAL1*, *SLC30A8*, *CDKN2A/B*, *HHEX/IDE*, *THADA*, *JAZF1*, *CDC123/CAMK1D*, *TSPAN8/LGR5*, *MTNR1B*, *KCNQ1*, *PROX1*, *GCK*, *DGKB/TMEM195*, and *CENTD2* may confer T2D risk most likely through impaired β -cell function,^{25, 37, 44, 51–60} although precise mechanisms are largely unclear. In the short list of insulin resistance-related loci, *PPARG* and *IRS1* have been well-recognized given their known biological function in insulin action and signaling. *ADAMTS9* and *GCKR* may also have an effect on insulin action,^{61–63} although the results from other studies are somewhat conflicting.^{57, 64, 65} In addition, *RBMS1* was also reported to be associated with insulin resistance.⁴³ *FTO* appears to confer T2D risk through its primary effect on adiposity,^{8, 9, 30, 31} however, two recent meta-analyses have shown that the association with T2D could not be fully explained by its effect on BMI.^{66, 67}

Recent genetic discoveries have implicated novel potential pathways in the development of T2D. The strongest association signal in *TCF7L2* highlights the important role of the Wnt-signaling pathway in β -cell function and insulin secretion.²⁰ The discovery of *SLC30A8* which encodes zinc transporter 8 suggests the importance of the role of insulin packaging and storage through β -cell zinc transporter⁶⁸ in the development of T2D. Several newly identified loci, such as *CDKAL1*, *CDKN2A/B*, and *CDC123*, have been involved in cell cycle regulation, and thus might be implicated in the pancreatic beta-cell regenerative process. Identification of *MTNR1B* as a T2D locus indicates a genetic link between circadian rhythm and glucose metabolism. In addition, genetic variants in *ADCY5*, encoding adenylate cyclase type 5, have been also associated with low birth weight,^{69, 70} providing new information on the observed relationship between low birth weight and increased risk of T2D in epidemiological studies.⁷¹

Genetic prediction in T2D

Genetic information is expected to have important clinical utility in the prediction of developing T2D. However, with the exception of risk allele *TCF7L2* which has a per-allele OR of ~1.4, most risk alleles in the newly identified T2D loci may only increase risk of T2D by 10–20%. Because of the modest effect sizes of each individual genetic variant, creating a genetic risk score by summing the number of risk alleles has been widely used in recent studies.^{72–81} It has been suggested that a genetic risk score that combines information from multiple genetic variants might be useful for identifying individuals with a particularly high risk for T2D.^{72–81} For example, a nested case-control study from the NHS and HPFS created a genetic risk score on the basis of 10 genetic variants and subgroups with extreme genetic risk profiles (4% of subjects with 0–7 risk alleles vs 5% of subjects with 15 risk alleles) showed a 4-fold difference in the risk of T2D.⁷⁷ In a population-based prospective study, 19 T2D genetic variants were used and individuals carrying 21 risk alleles or more (14% of the population) had about a 2-fold higher T2D risk compared with the reference group of 0–12 alleles (2 % of the population).⁷⁶

When using the area under the receiver operating characteristic (ROC) curves (AUCs) to evaluate discriminative accuracy of T2D by genetic variants (the AUC can range from 0.5 [total lack of discrimination] to 1.0 [perfect discrimination] and a test with AUC of greater than 0.75 is considered to be clinically useful), the results are less compelling. In most previous combined analyses of 10 to 20 T2D risk SNPs, the AUC for the genetic risk score alone was around 0.60,^{72, 75, 76, 78–80} while the AUC for conventional risk factors (such as age, gender, BMI, lifestyle, and family history of diabetes, etc.) was greater than 0.75.^{72, 73, 75, 77–80} The addition of the genetic risk score to the model of conventional risk factors slightly improved the discrimination of T2D.^{72, 73, 75–79} Thus, the prospects for individual prediction of T2D risk seem limited in the current stage. However, it should be noted that identified genetic loci account for only ~10% of T2D susceptibility in European-descent populations.⁴⁴

Gene-environment interactions

It is widely accepted that T2D is a product of the interplay between genetic and environmental factors. Although the genetic background of a certain population is relatively constant for many generations, it seems that the effects of genetic factors are amplified in the presence of certain environmental triggers. There have been dramatic changes in lifestyle and dietary habits over the past several decades, from a “traditional” style to a “Westernized” or “obesogenic” style, which is categorized by increased access to highly-palatable, calorie-dense food, and a sedentary lifestyle. In the HPFS, Qi *et al* found a significant interaction between a Western dietary pattern, derived from a principle component analysis of 40 food groups, and a genetic risk score of T2D susceptibility, based on 10 established SNP ($P = 0.02$).⁸² The multivariable ORs of T2D across increasing quartiles of the Western dietary pattern were 1.00, 1.23 (95% CI: 0.88, 1.73), 1.49 (1.06, 2.09), and 2.06 (1.48, 2.88) among men with a higher genetic risk score. Among those with a lower genetic risk score, the Western dietary pattern was not associated with diabetes risk. On the other hand, the genetic association with diabetes risk was more pronounced in individuals with a higher Western dietary pattern compared to those with a lower Western dietary pattern. This study illustrates the impact of gene-environment interactions on diabetes risk. In addition, several individual T2D loci, such as *TCF7L2*, *PPARG*, *SLC30A8*, and *GCKR*, have also been found to interact with dietary and lifestyle factors on T2D risk and related traits.^{83–86}

There are emerging studies reporting interactions between T2D loci and prenatal nutrition. In an earlier study, de Rooij et al. reported significant interactions between the *PPARG* Pro12Ala polymorphism and early malnutrition during mid-gestation on risk of impaired glucose tolerance and T2D.⁸⁷ Recently, Pulizzi et al. tested interactions between variants of nine T2D loci and birth weight, and they found that risk variants at the *HHEX*, *CDKN2A/2B*, and *JAZF1* loci significantly interacted with birth weight to predict future T2D.⁸⁸ In addition, in the Dutch Famine Birth Cohort, the *IGF2BP2* polymorphism showed an interaction with prenatal exposure to famine on glucose level.⁸⁹ These interaction analyses are related to the thrifty phenotype hypothesis⁹⁰ which states that malnutrition during fetal development leads to poor fetal and infant growth and predisposes individuals to T2D and other chronic metabolic disease. These data suggest that an individual's genetic background may modulate the response to prenatal nutrition and subsequently affect T2D risk caused by a hyper-caloric environment in later life.

With the identification of T2D genetic loci, some progress has also been made in characterizing gene-environment interactions that underlie T2D, however, many inconsistencies remain and significant findings require further replication and validation.⁹¹ Furthermore, studies focused on gene-environment interactions in relation to T2D are sparse in Asians and other ethnic groups.

Conclusions

Over a relatively short time, significant progress in understanding the genetics of T2D has been made by the waves of GWAS. To date, a total of 58 T2D genetic loci have been identified and most genetic variants seem to influence pancreatic β -cell function. Although the actual causal variants and biological function of most T2D genetic loci are largely unknown, many new loci provide new insights into the pathophysiology of T2D. In addition, the discovery of novel T2D susceptibility loci helps us understand the ethnic differences in diabetes risk and gene-environment interactions underlying T2D and provides new information in the clinical utility of genetic factors. More studies, such as fine-mapping, whole exome and genome sequencing, multiethnic meta-analysis, gene-gene and gene-environment interactions, epigenetics (DNA methylation analysis), and functional studies, are needed to identify new T2D loci, causal variants, and the underlying mechanisms and will help us better understand the differences in diabetes risk across ethnic groups.

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Figure 1. Genome-wide Manhattan plots for the DIAGRAM+ stage 1 meta-analysis

Data are based on a meta-analysis of eight T2D GWAS (8,130 T2D cases and 38,987 controls) in European populations, adapted from Voight *et al.*⁴⁴

Table 1

Type 2 diabetes susceptibility loci identified in European populations

Locus	SNP	Chr	Allele (+/-)	RAF*	OR	Probable mechanism
Candidate and large-scale association						
2000						
<i>PPARG</i> ⁶	rs1801282	3	C/G	0.92	1.14 ⁷⁻⁹	Insulin action
2003						
<i>KCNJ11</i> ¹¹	rs5219	11	T/C	0.50	1.14 ⁷⁻⁹	β -cell function
2006						
<i>TCF7L2</i> ¹⁸	rs7903146	10	T/C	0.25	1.37 ⁷⁻⁹	β -cell function
2007						
<i>WFS1</i> ¹³	rs10010131	4	G/A	0.60	1.11	β -cell function
<i>HNF1B (TCF2)</i> ¹⁷	rs4430796	17	A/G	0.47	1.10	unknown
2011						
<i>BCL2</i> ²¹	rs12454712	18	T/C	0.64	1.09	Unknown
<i>GATAD2A</i> ²¹	rs3794991	19	T/C	0.08	1.12	Unknown
GWAS						
2007						
<i>IGF2BP2</i> ⁷⁻⁹	rs4402960	3	T/G	0.29	1.14	β -cell function
<i>CDKAL1</i> ^{7-9, 23, 25}	rs10946398	6	C/A	0.31	1.12	β -cell function
<i>SLC30A8</i> ²⁴	rs13266634	8	C/T	0.75	1.12 ⁷⁻⁹	β -cell function
<i>CDKN2A/B</i> ⁷⁻⁹	rs10811661	9	T/C	0.79	1.20	β -cell function
<i>HHX/IDE</i> ²⁴	rs1111875	10	C/T	0.56	1.13 ⁷⁻⁹	β -cell function
<i>FTO</i> ^{8, 9, 23}	rs8050136	16	A/C	0.45	1.17	Obesity
2008						
<i>NOTCH2</i> ³²	rs10923931	1	T/G	0.11	1.13	Unknown
<i>THADA</i> ³²	rs7578597	2	T/C	0.92	1.15	β -cell function
<i>ADAMTS9</i> ³²	rs4607103	3	C/T	0.81	1.09	Insulin action
<i>JAZF1</i> ³²	rs864745	7	T/C	0.52	1.10	β -cell function

Locus	SNP	Chr	Allele (+/-)	RAF*	OR	Probable mechanism
<i>CDC123/CAMK1D</i> ³²	rs12779790 ³²	10	G/A	0.23	1.11	β-cell function
<i>TSPAN8/LGR5</i> ³²	rs7961581	12	C/T	0.23	1.09	β-cell function
<i>KCNQ1</i> ⁴⁴	rs231362	11	G/A	0.52	1.08	β-cell function
2009						
<i>IRS1</i> ³⁵	rs2943641	2	C/T	0.61	1.19	Insulin action
<i>MTNR1B</i> ^{36-38, 42}	rs10830963	11	G/C	0.30	1.09	β-cell function
2010						
<i>PROX1</i> ⁴²	rs340874	1	C/T	0.50	1.07	β-cell function
<i>BCL11A</i> ⁴⁴	rs243021	2	A/G	0.46	1.08	Unknown
<i>GCKR</i> ⁴²	rs780094	2	C/T	0.62	1.06	Insulin action
<i>RBMS1</i> ⁴³	rs7593730	2	C/T	0.83	1.11	Insulin action
<i>ADCY5</i> ⁴²	rs11708067	3	A/G	0.78	1.12	Unknown
<i>ZBED3</i> ⁴⁴	rs4457053	5	G/A	0.26	1.08	Unknown
<i>GCK</i> ⁴²	rs4607517	7	A/G	0.20	1.07	β-cell function
<i>DGKB/TMEM195</i> ⁴²	rs2191349	7	T/G	0.47	1.06	β-cell function
<i>KLF1</i> ⁴⁴	rs972283	7	G/A	0.55	1.07	Unknown
<i>TP53INP1</i> ⁴⁴	rs896854	8	T/C	0.48	1.06	Unknown
<i>TLE4 (CHCHD9)</i> ⁴⁴	rs13292136	9	C/T	0.93	1.11	Unknown
<i>CENTD2</i> ⁴⁴	rs1552224	11	A/C	0.88	1.14	β-cell function
<i>HMG2A</i> ⁴⁴	rs1531343	12	C/G	0.10	1.11	Unknown
<i>HNFI</i> ⁴⁴	rs7957197	12	T/A	0.85	1.07	Unknown
<i>PRCI</i> ⁴⁴	rs8042680	15	A/C	0.22	1.07	Unknown
<i>ZFAND6</i> ⁴⁴	rs11634397	15	G/A	0.56	1.06	Unknown
<i>DUSP9</i> ⁴⁴	rs5945326	X	G/A	0.12	1.27	Unknown

* Data were derived from HapMap EU or original studies.

SNP, single nucleotide polymorphism; Chr, chromosome; +/-, risk/reference allele; RAF, risk allele frequency; OR, odds ratio.