# Molecular Genetics of Diabetes Mellitus

**Nattachet Plengvidhya, M.D.*, Watip Boonyasrisawat, Ph.D.**, Prapaporn Jungtrakoon, M.Sc.**, Jatuporn Sujjitjoon, M.Sc.**, Pa-thai Yenchitsomanus, Ph.D.*****

**Division of Endocrinology and Metabolism, Department of Medicine, **Department of Immunology, ***Division of Medical Molecular Biology, Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

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Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[1] DM is a threat to the world population and a global burden in the 21st century. Its prevalence in adults worldwide was estimated to be 4.0% in the year 1995 and will have risen to 5.4% by the year 2025. There will be a 42% increase, from 51 to 72 million people affected, in the developed countries and a 170% increase, from 84 to 228 million people affected, in the developing countries.[2] It was estimated in 2000 that 9.6% (2.4 million) of Thai adults were affected with DM and 5.4% (1.4 million) had impaired fasting glucose[3]. These have indicated that DM is an enormous global public health problem and also an increasingly significant public health problem in Thailand. Since the disease is very heterogeneous, abnormality at different biological pathways can lead to hyperglycemia and subtypes of the disease requiring precise diagnostic criteria. Several research studies have concentrated on identifications of diabetic susceptibility genes. These efforts facilitate a better understanding in molecular pathogeneses and pathophysiologies underlying DM subtypes, thereby leading to the development of appropriate and effective therapeutic approaches.

## Classification and Pathogenesis of Diabetes Mellitus – Vital for Genetic studies

A major requirement for epidemiological and clinical research and for clinical management of diabetes is an appropriate system of classification that provides a framework within which to identify and differentiate its various forms and stages. DM generally presents in two major forms, type 1 diabetes (T1D) and type 2 diabetes (T2D). T2D is more common, accounting for approximately 90% of diabetic cases. The onset of T1D is in childhood while that of T2D is predominantly after 40 years of age and generally occurs in obese people. T1D (also autoimmune diabetes mellitus) is usually caused by autoimmune destruction of islet beta cells in the pancreas. The destruction of islet beta cells causes insulin deficiency and thereby dysregulation of anabolism and catabolism. T1D has a characteristic feature for most of the autoimmune diseases.[4] (i) It is associated with specific human leukocyte antigens (HLA) class II haplotypes (particularly HLA DRB1*04–DQB1*0302, but also HLA DRB1*03–DQB1*0201), (ii) autoantibodies against autoantigens of β-cells are found (GAD65, IA-2, ICA, IAA), and (*iii*) mononuclear cell infiltration of the pancreatic islets can be detected histologically. However, the exact mechanism involved in the initiation and progression of β cell destruction in T1D is still un clear.

While most T1D is characterized by the presence of autoantibodies identifying the autoimmune process that leads to β-cell destruction and insulin deficiency (Fig 1), T2D includes the most prevalent form of diabetes which results from insulin resistance or insulin secretory defect or both (Fig 2).[5] Generally, exogenous insulin is not required for the survival of T2D patients. This form of diabetes frequently goes undiagnosed for many years because hyperglycemia developed gradually. The earlier stage is often not severe enough to cause noticeable symptoms. Obesity is one of the principal risk factors for T2D. Weight gain leads to insulin resistance through several mechanisms. Insulin resistance places a greater

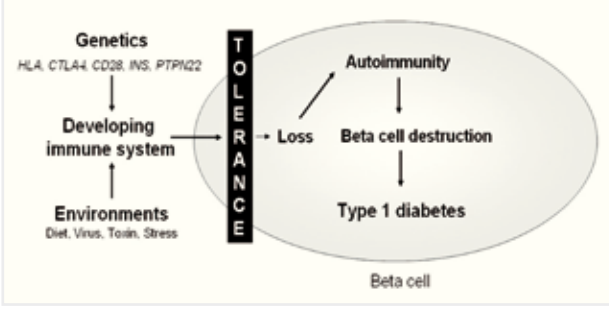


**Fig 1.** Pathogenesis of type 1 diabetes (T1D). Genetic predisposition and environmental factors are involved in failure of tolerance to β-cell (self) antigens and autoimmune de struction of pancreatic β-cells leading to T1D.

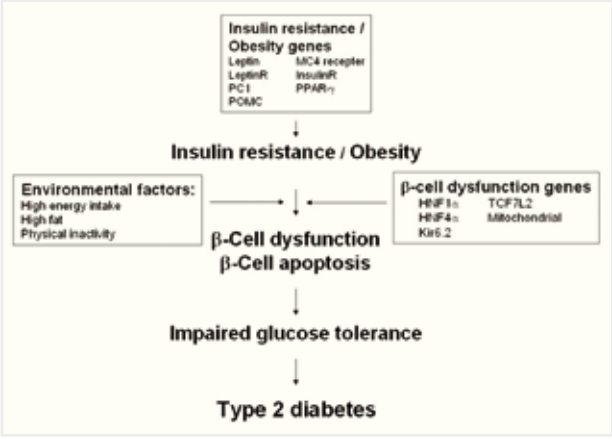


**Fig 2.** Pathogenesis of type 2 diabetes (T2D). The interaction of diabetic susceptible genes (causing insulin resistance, obesity, and β-cell defects) and environmental factors leads to relative insulin insufficiency. Impaired glucose tolerance and T2D are developed when pancreatic β-cells are unable to adequately compensate for the requirement of insulin in obesity and/or insulin resistance.

demand on the pancreatic capacity to produce insulin, which also declines with age, leading to the development of diabetes. Physical inactivity, both a cause and consequence of weight gain, also contributes to insulin resistance.[6,7]

Other specific types of DM, including several monogenic defects in β-cell function and a non-genetic form, account for approximately 1%-2% of cases. Maturity onset diabetes of the young (MODY) is one of monogenic form that is characterized by onset of hyperglycemia at an early age (generally before age 25). The term maturity-onset diabetes of the young was based on the old classification of diabetes into juvenile-onset and maturity-onset diabetes. The American Diabetes Association and the World Health Organization have introduced a revised, cause-based classification for diabetes. MODY is now defined as a genetic defect in β-cell function with subclassification according to the gene involved.[1] The characteristics used to differentiate T2D from T1D and MODY are shown in Table 1.

## Type 1 Diabetes (T1D)

T1D is a complex and polygenic disease due to gene-environment interactions. The role of the genetic background of diabetes has been extensively investigated. However, final conclusions have not yet been reached. Family and twin studies have shown that genetic factors are important contributors to the disease risk. There is significant familial clustering of T1D with an average prevalence risk of 7% in siblings and 6% in a child of affected parents, compared to 0.4% in the general population. The degree of clustering of disease in families can be estimated from the relative risk (λs) which is the ratio between the prevalence of disease among the patients' siblings and the prevalence of the disease in the population. If this ratio (λs) is close to 1, there is no evidence for familial clustering. For T1D, the degree of familial clustering λs is about 15 (6%/0.4%), which means that if a family has a child with T1D, then the other siblings have a 15 times greater risk of developing diabetes than the general population.[8]

Although more than 18 T1D-predisposing genes have been reported to date, only the major histocompatibility complex (HLA) region on chromosome 6p21 (IDDM1) and the insulin (INS) gene on chromosome 11p15 (IDDM 2) have been conclusively associated with susceptibility to T1D. Alleles at the human leukocyte antigen (HLA) locus explain up to 50% of the familial clustering of T1D through a large variety of protective and predisposing haplotypes.[9]

However, it has recently been shown that there are other important loci associated with T1D but with much smaller effects than *HLA* and *insulin* (INS) genes. These genes encode protein tyrosine phosphatase (PTPN22), cytotoxic T-lymphocyte antigen 4 (CTLA4), interleukin-2 receptor A (IL2RA), interferon-induced helicase (IFIH1), C-type lectin domain family (CLEC-16A) and cytochrome P450, Subfamily XXVIIb, polypeptide 1 (CYP27B1)[10]. In addition, recent genome-wide association studies (GWAS) have uncovered two additional solidly replicated loci that, have not yet been mapped to individual genes (Table 2).

By identifying new loci and reanalysis of previous studies with the help of more powerful genetic analysis tools, it is highly likely to shed more light on the complex field of the genetics of T1D and to further understand the molecular pathophysiology of the disease, which will allow us eventually to treat or prevent it.

## Type 2 Diabetes (T2D)

Clearly, genetic variants predispose an individual toward reduced insulin secretion or increased insulin resistance. Sequence variations of several candidate genes involved in insulin sensitivity, β-cell function and obesity were investigated by a genetic case-controlled association approach. More than 40 different genes have been reported to be associated with T2D but few have been replicated in additional populations.[9] Study of *peroxisome proliferators-activated receptor-gamma*

**TABLE 1.** Differentiation of MODY from T2D and T1D (adapted from Hattersley et al[30]).

| Characteristics | T1D | T2D | MODY |
|---|---|---|---|
| Relative frequencies | 90% | <10% | 1-3% |
| Genetics | Polygenic | Polygenic | Monogenic |
| Clinical presentation onset | Acute | Variable | Variable |
| Age | Throughout childhood | Usually pubertal or later | Often postpubertal |
| Obesity | Same risk as general population | Common | Same risk as general population |
| Ketosis | Common | Rare | Rare |
| Antibodies to islets antigens | Positive ICA, GAD, IA2 | Rare | No |
| Associated autoimmune disease | Yes | No | No |
| Parent with diabetes | 2-4% | 40-80% | 90% |

**TABLE 2.** T1D-susceptible loci (modified from Ounissi-Benkalha and Polychronakos[10]).

| Locus | Gene | Odd ratio Het | Hom | Postulated mechanism |
|---|---|---|---|---|
| 6p21 *(IDDM1)* | *HLA DR-DQ* | 0.02-11.4 | 0.02-49.2 | Present exogenous antigen processed by APCs, with some antigen specificity. Predisposing alleles might bind autoantigens poorly, compromising adaptive self tolerance. |
| | *HLA-A* | 0.29-1.23 | | Present endogenously synthesize antigen (e.g. viral) by all cells. |
| | *HLA-B* | 0.73-3.6 | | |
| 11p15 *(IDDM2)* | *INS* | 2.68 | 3.27 | Modulation of thymic expression and central tolerance to insulin. |
| 1p13 | *PTPN22* | 1.95 | 4.16 | Moderates TCR signaling by dephosphorylation. Gain of function might inhibit proper development of tolerance. |
| 2q31 *(IDDM12)* | *CTLA4* | 1.14 | 1.5 | Moderates T-cell activation. Functional effect of locus to be determined. |
| 10p15 | *IL2RA* | 1.87 | 3.89 | Modulation of the effect of IL2 on regulatory and/or effector T lymphocytes. |
| 2q24 | *IFIH1* | 1.18 | 1.37 | Triggers interferon response upon recognition of viral RNA. Might be involved in infectious etiology of T1D. |
| 16p13 | *CLEC16A* | 1.29 | 1.42 | Function unknown. Contains C-lectin and ITAM domains. |
| 18q11 | *PTPN22* | 1.33 | 1.61 | Phosphotyrosine phosphatase. Role likely similar to *PTPN2.* |
| 12q24 | | 1.24 | 1.74 | Not mapped to specific gene. |
| 12q13 | | 1.31 | 1.58 | Not mapped to specific gene. |

(*PPARγ*), which encodes a transcription factor and plays a central role in adipocyte development, is the most widely reproduced association.[11] The Pro12Ala polymorphism in *PPARγ* had been conclusively associated with common T2D.[12] Strong candidate genes for T2D are *ATP-binding cassette, sub-family C, member 8 (ABCC8)* encoding sulfonylurea receptor (SUR1), a drug target for an oral hypoglycemic agent − sulfonylurea, and *potassium inwardly-rectifying channel, subfamily J, member 11 (KCNJ11)* encoding Kir6.2, the gene in the same region of chromosome 11. Both proteins interact physically and functionally to regulate the potassium inward rectifier current and β-cell depolarization, the trigger for insulin release.[13]

Several T2D genome-wide association studies (GWAS) were reported in early 2007, initially in Europeans and later in more diverse populations. The combined data of the traditional candidate-gene approach together with recent information from five GWAS, as well as a partial meta-analysis that encompasses three of them (Table 3) have confirmed known T2D loci and introduced at least six novel diabetes genes. Of note, *TCF7L2* has been replicated as the genetic locus with the strongest signal. The first GWAS was performed in a French population and reported in early 2007.[14] It confirmed the impact of *TCF7L2* as a T2D susceptibility locus and also identified hematopoietically expressed homeobox *(HHEX)* and solute carrier family 30 member 8 *(SLC30A8)* as potential novel T2D loci. *HHEX* is thought to be involved in β cell development or function. SLC30A8, a zinc transporter gene initially cloned and sequenced in 2004, is expressed exclusively in pancreatic β cells, where it transports zinc from the cytoplasm into insulin secretory vesicles. This is a critical step in the final biosynthetic pathway of insulin production and secretion. Following this initial report, four GWAS were published at the same time. The deCODE group and collaborators[15] confirmed the strong signal of TCF7L2 and replicated the HHEX and SCL30A8 findings. The novel T2D susceptibility loci, CDK5 regulatory subunit associated protein 1−like 1 *(CDKAL1)* was identified in this study. This gene affects CDK5/CDK5R1 activity, and in so doing, may lead to β cell degeneration. The Diabetes Genetics Initiative (DGI)[16], the Wellcome Trust Case Control Consortium (WTCCC)[17], and the Finland−United States Investigation of NIDDM Genetics (FUSION)[18], studies represent, in aggregation, more than 32,000 individuals which confirmed the impact of *TCF7L2, KCNJ11, PPARG* loci as well as *HHEX, SCL30A8* and *CDKAL1* on the risk of development of T2D. These studies also discovered the novel diabetes loci; insulin-like growth factor 2 mRNA binding protein 2 *(IGF2BP2)* and cyclin-dependent kinase inhibitor 2B *(CDKN2B).*

## Monogenic Diabetes

Some of the most compelling evidence that genetic variation can cause glycemic dysregulation comes from the clinical and genetic description of monogenic diabetes, including maturity-onset diabetes of the young (MODY), insulin resistance syndromes, mitochondrial diabetes, and neonatal diabetes. Although uncommon, these diabetic subtypes provide a framework for understanding and investigating the complex genetics underlying T2D.

### Maturity-Onset Diabetes of the Young

The well-defined mode of inheritance with high penetrance and the early age of onset of diabetes allow the collection of multigenerational pedigrees, making MODY an attractive model for genetic studies. MODY is not a single entity but is a heterogeneous disease with regard to genetic, metabolic, and clinical features. The underlying pathophysiology of MODY is an insulin secretion defect usually without insulin resistance.[19] The concerted application of modern genetic linkage and positional cloning techniques led to the successive identification of six MODY genes including hepatocyte nuclear *factor-4α (HNF-4α), glucokinase (GCK), hepatocyte nuclear factor-1α (HNF-1α), insulin promotor factor-1 (IPF-1), hepatcyte nuclear factor-1β, (HNF-1β), and neurogenic dfferentiation 1/β-cell E-box transactivat or 2 (NeuroD 1/β 2).* Moreover, additional MODY genes remain to be discovered, since there are MODY fami-

**TABLE 3.** Genetic loci associated with T2D that have achieved genome wide significance (modified from Moore and Florez23).

| Marker (location) | Nearest gene | Function | Risk allele | Odd Ratio (p-value) Sladek *et al.* (n=6,794) | deCODE (n=10,056) | DGI (n=13,781) | WTCCC (n=13,965) | FUSION (n=4,808) | Meta-analysis* (n=32,554) |
|---|---|---|---|---|---|---|---|---|---|
| **Previously known** | | | | | | | | | |
| rs7903146 (Intron) | *TCF7L2* | Transcription factor; risk allele impairs insulin secretion | T | 1.65 ($3.3 \times 10^{-10}$) | 1.38 ($1.9 \times 10^{-10}$) | 13.8 ($2.3 \times 10^{-31}$) | 1.37 ($6.7 \times 10^{-13}$) | 1.34 ($1.4 \times 10^{-8}$) | 1.37 ($1.0 \times 10^{-48}$) |
| rs5219 (Exon) | *KCNJ11* | Kir6.2 potassium channel; risk allele impairs insulin secretion | T | 1.34 (0.074) | | 1.15 ($1.0 \times 10^{-7}$) | 1.15 ($1.3 \times 10^{-3}$) | 1.11 (0.014) | 1.14 ($6.7 \times 10^{-11}$) |
| rs1801282 (Exon) | *PPARG* | Nuclear hormone receptor; target for thiazolidinediones | C | 1.22 (0.11) | | 1.09 (0.019) | 1.23 ($1.3 \times 10^{-4}$) | 1.20 ($1.4 \times 10^{-3}$) | 1.14 ($1.7 \times 10^{-6}$) |
| **Identified by GWAS** | | | | | | | | | |
| rs4402960 (Intron) | *IGF2BP2* | Growth factor binding protein; pancreatic development | T | | | 1.17 ($1.7 \times 10^{-9}$) | 1.11 ($1.6 \times 10^{-4}$) | 1.18 ($2.4 \times 10^{-4}$) | 1.14 ($8.9 \times 10^{-16}$) |
| rs10811661 (Intergenic) | *CDKN2B* | Cyclin dependent kinase inhibitor and p15 tumor suppressor; islet development | T | | | 1.20 ($5.4 \times 10^{-8}$) | 1.19 ($4.9 \times 10^{-7}$) | 1.20 ($2.2 \times 10^{-3}$) | 1.2 ($7.8 \times 10^{-15}$) |
| rs7754840 (Intron) | *CDKAL1* | Homologous to CDD5RAP1, CDK5 inhibitor; islet glucotoxicity sensor | C | | 1.2 ($7.7 \times 10^{-9}$) | 1.08 ($2.4 \times 10^{-3}$) | 1.16 ($1.3 \times 10^{-8}$) | 1.12 ($9.5 \times 10^{-3}$) | 1.12 ($4.1 \times 10^{-11}$) |
| rs1111875 (Intergenic) | *HHEX* | Pancreatic transcription factor; pancreatic development | C | 1.21 ($8.6 \times 10^{-6}$) | 1.17 (0.001) | 1.14 ($1.7 \times 10^{-4}$) | 1.13 ($4.6 \times 10^{-6}$) | 1.10 (0.025) | 1.13 ($5.7 \times 10^{-10}$) |
| rs13266634 (Exon) | *SLC30A8* | Beta cell zinc transporter ZnT8; insulin biosynthesis | C | 1.18 (5.0 x 10-7) | 1.19 (0.001) | 1.07 (0.047) | 1.12 ($7.0 \times 10^{-5}$) | 1.18 ($7.0 \times 10^{-5}$) | 1.12 ($5.3 \times 10^{-8}$) |

*Meta-analysis of DGI, WTCCC and FUSION

lies which diabetes does not cosegregate with the known MODY loci, referred to as MODY-X.

The prevalence of MODY is estimated at less than 5% of patients who have T2D in most white populations. The prevalence of different subtypes of MODY varies greatly as demonstrated from studies in the British, French, German, and Spanish family cohorts. The estimated prevalence of MODY-X is 15-20% in European families[20] and 60-80% in Chinese[21] and Japanese families[22]. Analysis of genetic variability of MODY genes in Thai diabetic patients performed by Siriraj Diabetes Research Group (SiDRG) showed that sequence variations of the six known MODY genes account for a small proportion of both classic MODY (19%) and early-onset type 2 diabetes patients (10%) suggesting that MODY-X is also frequent in the Thai population.

### Insulin Resistance Syndromes and Lipodystrophies

These syndromes are characterized biochemically by hyperinsulinemia and insulin resistance in fat, muscle, and liver. The insulin receptor was a logical initial candidate gene for the severe hyperinsulinemia described in index patients. The most severe form of insulin resistance is Donahue syndrome or leprechaunism, named for the dysmorphic appearance of the affected infants. The Rabson-Mendenall syndrome is characterized by pineal hyperplasia, acanthosis nigricans, accelerated growth, and dental dysplasia. Mutations of the insulin receptor gene allow incomplete receptor activation. The lipodystrophies are characterized by dysregulation of fat storage. Adipose tissue is deposited inappropriately in muscle and liver rather than the usual subcutaneous compartment.[23]

### Mitochondrial Diabetes

Mitochondrial diabetes is another rare variant of monogenic diabetes. Maternally inherited diabetes and deafness (MIDD) is caused by an alanine-to-guanine mutation in the gene encoding the tRNA for leucine. This defect leads to ineffective oxidative phosphorylation.[23]

### Neonatal Diabetes

Neonatal diabetes, which usually presents in the initial days or months of life, can be transient (resolving at a median of 12 weeks) or permanent.

Most cases of transient neonatal diabetes mellitus (TNDM) result from imprinting mutations of the *ZAC* and *HYMAI* genes on chromosome 6q24. This type of neonatal diabetes usually remits in childhood but is associated with an increased risk of T2D in adulthood. Permanent neonatal diabetes mellitus (PNDM), traditionally treated with insulin, has recently been shown to be associated with activating mutations in the *KCNJ11* gene, which encodes the islet ATP-sensitive potassium channel Kir6.2. The severity of the mutation correlates with the clinical phenotype—some KCNJ11 defects result in PNDM, and even more severe genetic mutations result in the DEND syndrome (developmental delay, epilepsy, neonatal diabetes). Mutations in this gene appear to be the most common cause of neonatal diabetes and account for about one third of PNDM cases.

### Genetics of Diabetic Complications

A principal objective of the clinical management of diabetes is the prevention of long-term vascular complications. The complications of diabetes can be broadly categorized as microvascular (including retinopathy and nephropathy) and macrovascular (affecting the coronary, cerebral, and peripheral arterial vasculature). These complications can result in potential loss of vision, renal failure, coronary heart disease, stroke, foot ulcers, amputation, Charcot joints, and autonomic neuropathy. These complications are common to both T1D and T2D.

Not only diabetes but also their complications are influenced by genetic factors. There is mounting evidence for the role of genetic factors in several diabetic complications, particularly diabetic nephropathy (DN). DN is the most common cause of end-stage renal disease (ESRD) and accounts for a significant increase in morbidity and mortality in patients with diabetes. The familial clustering of overt DN and diabetic ESRD has been observed widely in multiple racial and ethnic groups, with the earliest reports of familial aggregation of diabetic kidney disease in patients with T1D. Family members with diabetes, even in the absence of clinical nephropathy, demonstrate similar patterns of glomerular involvement.

Accelerated atherosclerosis is a hallmark of macrovascular disease in both T1D and T2D. Although the pathophysiology of atherosclerosis in T1D has not been fully elucidated, the current concept supports a model in which circulating factors associated with the perturbed metabolic milieu of T1D (e.g. hyperglycaemia, glycation, and oxidation products) cause endothelial dysfunction, which in turn leads to vasoconstrictive, proinflammatory, and pro-thrombotic changes that contribute to atherosclerotic plaque development and an enhanced potential for thrombosis after plaque rupture.[24]

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes. The evaluation of retinopathy enables clinicians a unique opportunity to directly visualize and assess the actual morphology of diabetic microvascular damage. Extensive studies have shown that people with diabetic retinopathy have excess risks of systemic vascular complications, including subclinical and clinical stroke, coronary heart disease, heart failure, and nephropathy. There is also emerging evidence which suggests that diabetic retinopathy may share common genetic linkages with systemic vascular complications.[25]

Hundreds of loci have been studied so far in order to explain genetic susceptibility to diabetic complications. Most loci identified to date have not been replicated probably due to the complex etiologies of all diabetic complications. Recent information indicated that the most intriguing genes are those encoding aldose receptor, advanced glycation end products receptor, vascular endothelial growth factor, intercellular adhesion-molecule 1, β3-adrenergic receptor gene, hemochromatosis, reductase and α2β1 integrin, which may represent a fruitful area for further genetics studies of DN and DR.[26,27]

Recently, advanced glycation end-products (AGEs) have been shown to induce oxidative stress, increase inflammation by promoting NFkB activation, and enhance extracellular matrix accumulation. These biological effects translate to accelerated plaque formation in diabetes as well as increased cardiac fibrosis with consequent effects on cardiac function.[28] Several studies suggested that inflammation would be an essential component of T2D and its complications. An increased systemic inflammation in high glucose milieu is important in the pathogenesis of coronary artery disease (CAD) in patients with T2D. Recently, the role of genetic variability of *A20/TNFAIP3* has been show to modulate the CAD risk in T2D, which was mediated by allelic differences in *A20* expression.[29] The understanding of genetic factors predisposing to diabetic complications would help to unveil their pathogenesis and may lead to the development of novel preventive measures.

## CONCLUSION

Diabetes mellitus affects more than 150 million people worldwide, and this number is expected to double within the next two decades. The genetic susceptibility to the disease and an individual genetic signature remain incompletely understood. However, during the past decade, genetic analysis of DM and its complications have been extremely productive. Multiple genes have been identified especially through a series of genome-wide association studies (GWAS). It is of important that results from various genetic studies must be replicated in different populations in the validation of individual findings. Demonstration of functional modifications of the encoded variant proteins will also be an important evidence to support identified susceptible genes – the step following GWAS. Understanding the complex interactions among genetic profiles, individual lifestyles, and environmental factors lies at the core of effective diabetes treatment. The successful means to identify the disease at an early stage, changes of life-style, and dietary behavior are important for prevention and control of the disease. It is expected that characterization of the genetic factors involved in the development of DM and its complications will lead to the understanding of their molecular pathogenesis and the development of novel therapeutic approaches.

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