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TOPIC HIGHLIGHT

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Recent advances in the molecular genetics of type 2 diabetes mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is a complex disease in which both genetic and environmental factors interact in determining impaired β-cell insulin secretion and peripheral insulin resistance. Insulin resistance in muscle, liver and fat is a prominent feature of most patients with T2DM and obesity, resulting in a reduced response of these tissues to insulin. Considerable evidence has been accumulated to indicate that heredity is a major determinant of insulin resistance and T2DM. It is believed that, among individuals destined to develop T2DM, hyperinsulinemia is the mechanism by which the pancreatic β-cell initially compensates for deteriorating peripheral insulin sensitivity, thus ensuring normal glucose tolerance. Most of these people will develop T2DM when β-cells fail to compensate. Despite the progress achieved in this field in recent years, the genetic causes of insulin resistance and T2DM remain elusive. Candidate gene association, linkage and genome-wide association studies have highlighted the role of genetic factors in the development of T2DM. Using these strategies, a large number of variants have been identified in many of these genes, most of which may influence both hepatic and peripheral insulin resistance, adipogenesis and β-cell mass and function. Recently, a new gene has been identified by our research group, the *HMGA1* gene, whose loss of function can greatly raise the risk of developing T2DM in humans and mice. Functional genetic variants of the *HMGA1* gene have been associated with insulin resistance syndromes among white Europeans, Chinese individuals and Americans of Hispanic ancestry. These findings may represent new ways to improve or even prevent T2DM.

Key words: Genome-wide association study; Candidate gene; Genetic variants; High-mobility group A1; Insulin resistant diabetes

Core tip: Despite the progress in clinical and laboratory investigations, the fundamental cause of type 2 diabetes mellitus (T2DM) remains uncertain. Candidate gene, linkage and genome-wide association studies have highlighted the role of genetics in the development of T2DM. Using these strategies, a large number of variants have been identified in many genes, most of which may influence an individual's risk of developing T2DM. In this review, we compile information on genetic factors that influence the risk of T2DM. In addition, we discuss the results from recent studies on the role of HMGA1 on the issue, which might be important for future breakthroughs in this field.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic endocrine

and metabolic disease that is often associated with being overweight or frank obesity. It affects millions of people worldwide, with a rapidly increasing incidence and prevalence[1,2]. The latest estimate from the International Diabetes Federation (http://www.idf.org) is equivalent to a global prevalence rate of 8.4% of the adult population, while worldwide diabetes cases hit a new record at 382 million in 2013. Among the determinants of this steadily increasing trend is the combination of genetic and environmental factors responsible for either a positive energy balance resulting in body fat accumulation and weight gain and/or a reduced energy expenditure from a reduction in physical activity and a sedentary lifestyle. Despite extensive attempts at clinical management of T2DM, many diabetic patients will develop a wide variety of long-term complications, including retinopathy, nephropathy and cardiovascular diseases that are among the most frequent causes of morbidity and mortality in affected people, whose effective prevention and treatment require enormous efforts and funding[3]. Typically, T2DM is presented as a common, heterogeneous, complex disease in which both predisposing genetic factors and precipitating environmental factors interact together and cause hyperglycemia, which constitutes the primary hallmark of T2DM[4,5]. Although still poorly understood, the role of genetics in T2DM is well documented. This is supported by a series of evidence, including the strong familial aggregation of the disease, in which the risk of developing T2DM is 40% for those who have an affected parent (higher if the mother rather than the father) and 70% if both parents are diabetics[6]. The highest risk in first-degree relatives, compared to the general population, persists even after removal from the family of origin, for example, as a result of adoption. Furthermore, in identical monozygotic twins (with identical genetic makeup), the concordance rate for the disease approaches 100%, much higher than that seen in non-identical (dizygotic) twins or among siblings[7]. Genetic predisposition in T2DM is also supported by the observation that differences in disease prevalence rates exist among populations, even after migration of entire ethnic groups to another country, thus independent from the environmental influences[8].

On the other hand, the role of environmental factors in influencing susceptibility to T2DM is equally well known. Among these factors are increased caloric intake and a sedentary lifestyle, two conditions common in populations with a higher standard of living and a more westernized lifestyle, responsible for most of the excess weight and obesity in the modern adult's life[9]. The spread of the western way of life in developing countries also explains the epidemic explosion of the disease[1,2], whereas the existing epidemiological data show that the spatial and temporal distribution of T2DM in the geographical areas examined is comparable to the trend of being overweight and obesity[10]. The excess weight causes insulin resistance, which represents the initial step in the natural history of T2DM. Initially, in individuals destined to become diabetic, pancreatic β-cells compensate for the insulin resistance by secreting increased levels of insulin, thus ensuring post-prandial euglycemia[11]. Hyperglycemia in insulin resistant subjects develops later when the β-cells fail to compensate. Thus, from a pathophysiological standpoint, T2DM is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by the pancreatic β-cells. As supported by numerous studies in the literature[12,13], both defects are the result of a complex interaction between genetic and environmental factors (Figure 1), including chemical agents (calcium and zinc ions) and polluting organic substances that are suspected to play a role in amyloid fiber formation in pancreatic β-cells, thus contributing to the pathology of T2DM[14-17]. The involvement in the pathogenesis of T2DM of multiple genes that interact with each other in an epistatic manner may explain why, despite the enormous efforts made to date, the identification of genetic determinants responsible for an increased susceptibility to T2DM still remains unsolved[18,19].

The present review aims to give an overview of the recent findings in this context. We also discuss the results from some recent studies which might be important for future breakthroughs in this field.

GENETIC STUDIES

Over the past few years, various international research centers have been involved in the study and identification of genes predisposing to T2DM using various methods of investigation. Linkage analysis was used to identify potential genes associated with the disease, starting from the analysis of families and then studying a small number of individuals genetically related to each other. Genotyping for genetic markers in family members with and without T2DM has allowed the identification of DNA regions containing loci associated with disease risk. Thanks to this method, the association of T2DM with the calpain-10 (*CAPN10*) gene[20] was initially identified and later its association with the transcription factor 7-like 2 (*TCF7L2*) gene[21], whose genetic variants in affected individuals increase the risk of diabetes approximately 1.5 times[19].

Another approach used was to search for genetic variants within functional candidate genes encoding for protein(s) with important implications for glucose homeostasis and positional candidate genes that have a genetic association on the basis of a previous linkage study. This experimental strategy is applied to population studies rather than studies of families. Association studies of functional candidate genes represent one of the most powerful approaches as the pathogenetic mechanism of any genetic abnormality would be easily explained. The limit of this strategy, however, is constituted by the fact that it allows focused attention on a single gene at a time. Although many studies have reported associations of functional and positional candidate genes with T2DM, only some of these showed a significant and reproducible association with the disease (Table 1).

From 2007 onwards, the list of candidate genes has grown considerably, largely due to genome-wide associa-

Table 1 Type 2 diabetes mellitus susceptibility genes

Gene	Chr	Odds ratio	RAF	Study	Function and probable mechanism	Ref
ADAMTS9	3	1.09-1.05	0.68-0.81	MA	Metalloproteinase/Insulin action	[22–24]
ADCY5	3	1.12	0.78	MA	Adenylyl cyclases/Insulin action	[25]
ANK1	8	1.09	0.76	MA, CC	Cell stability/β-cell function	[26–28]
ANKRD55	5	1.08	0.7	MA, CC	Insulin action	[26,27]
ANKS1A	6	1.11	0.91	GWAS	Pathway regulator/Unknown	[29]
ARAP1	11	1.08-1.14	0.81-0.88	GWAS, MA	Actin cytoskeleton modulator/β-cell function	[22,24]
BCAR1	16	1.12	0.89	MA, CC	Docking protein/β-cell function	[26,27]
BCL2	18	1.09	0.64	GWAS	Cell death regulator/Unknown	[24]
BCL11A	2	1.08-1.09	0.46	MA	Zinc finger/β-cell function	[22]
CAMK1D	10	1.07-1.11	0.18	LA, MA	Protein kinase/β-cell function	[22–24]
CDC123					Mitotic protein/β-cell function	
CAPN10	2	1.09-1.18	0.73-0.96	MA	Calpain cysteine protease/Insulin action	[30–33]
CDKAL1	6	1.10-1.20	0.27-0.31	GWAS, MA	β-cell function	[24,34–36]
CDKN2A	9	1.19-1.20	0.82-0.83	GWAS	Cyclin-dependent kinase inhibitor/β-cell function	[24,34,35]
CDKN2B						
CENTD2	11	1.08-1.13	0.81-0.88	GWAS	β-cell function	[22,24]
CHCHD9	9	1.11-1.20	0.93	MA	Unknown	[22]
TLE4						
CILP2	19	1.13	0.08	MA, CC	Unknown	[26,27]
DGKB	7	1.04-1.06	0.47-0.54	MA	Diacylglycerol kinase/Insulin action	[24,25]
DUSP9	X	1.09-1.27	0.12-0.77	MA	Phosphatase	[22,24]
FOLH1	11	1.10	0.09	GWAS	Transmembrane glycoprotein/Unknown	[24]
FTO	16	1.06-1.27	0.38-0.41	GWAS, MA	Metabolic regulator/Insulin action	[24,37]
GATAD2A	19	1.12	0.08	GWAS	Transcriptional repressor/Unknown	[24]
GCK	7	1.07	0.20	MA	Glucokinase/Insulin action	[25]
GCKR	2	1.06-1.09	0.59-0.62	MA	Glucokinase regulator/Insulin action	[24,25]
GIPR	19	1.10	0.27	GWAS	G-protein coupled receptor/Unknown	[24]
GRB14	2	1.07	0.60	MA, GCS	Adapter protein/Insulin action	[26,27]
HFE	6	1.12	0.29	MA	Membrane protein/Unknown	[38]
HHEX	10	1.12-1.13	0.53-0.60	AL, MA	Transcriptional repressor/	[22,24,34,39]
IDE					Intracellular insulin degradation/	
KIF11					Motor protein	
HMG20A	15	1.08	0.68	MA, GCS	Chromatin-associated protein/Unknown	[26,27]
HMGA1	6	1.34-15.8	0.10	GCS	Transcriptional regulator/Insulin action	[40-42]
HMGA2	12	1.10-1.20	0.09-0.10	MA	Transcriptional regulator	[22,24]
HNF1A	12	1.07-1.14	0.77-0.85	MA	Pancreatic and liver transcriptional activator	[22,24]
HNF1B	17	1.08-1.17	0.47-0.51	GCS, MA	Transcription factor/β-cell function	[22,24]
IGF2BP2	3	1.14	0.29-0.32	GWAS, MA	Binding protein/β-cell function	[22,24,34,35]
IRS1	2	1.09-1.12	0.64-0.67	GCS, MA	Insulin signaling element/Insulin action	[22,24,43]
JAZF1	7	1.10	0.52	MA	Zinc finger/β-cell function	[22,23]
KCNJ11	11	1.09-1.14	0.37-0.47	GCS, MA	Potassium channel/β-cell function	[22,24,34,44]
KCNQ1	11	1.08-1.23	0.44	GWAS	Potassium channel/β-cell function	[22,45,46]
KLF14	7	1.07-1.10	0.55	MA	Transcription factor/Insulin action	[22]
KLHDC5	12	1.10	0.80	MA, CC	Mitotic progression and cytokinesis/Unknown	[26,27]
LAMA1	18	1.13	0.38	GWAS	Cellular migration mediator/Unknown	[29]
MC4R	18	1.08	0.27	MA, CC	G-protein–coupled receptor/Unknown	[26,27]
MTNR1B	11	1.05-1.08	0.28-0.30	GWAS, MA	Melatonin receptor/β-cell function	[24,47-49]
NOTCH2	1	1.06-1.13	0.10-0.11	MA	Membrane receptor	[22-24]
PPARG	3	1.11-1.17	0.85-0.88	GCS, MA	Nuclear receptor/Insulin action	[22,24,34,50]
PRC1	15	1.07-1.10	0.22	MA	Cytokinesis regulator	[22]
PROX1	1	1.07	0.50	MA	Homeobox transcription factor/Insulin action	[25]
PTPRD	9	1.57	0.10	GWAS	Protein tyrosine phosphatase	[51]
RBMS1	2	1.11-1.08	0.79-0.83	MA	DNA modulator/Insulin action	[24,52]
SLC2A2	3	1.06	0.74	GWAS	Glucose sensor/β-cell function	[24]
SLC30A8	8	1.11-1.18	0.65-0.70	GWAS, MA	Zinc efflux transporter/β-cell function	[22,24,25,34,53]
SREBF1	17	1.07	0.38	GWAS	Lipid transcriptional regulator/Unknown	[24]
SRR	17	1.28	0.69	GWAS	Serine racemase	[51]
TCF7L2	10	1.31-1.71	0.26-0.30	LA, MA,GWAS	Participates in the Wnt signaling pathway/β-cell function	[21,22,24,34]
THADA	2	1.15	0.90	MA	Thyroid adenoma-associated protein/β-cell function	[22-24]
TH/INS	11	1.14	0.39	GWAS	Catecholamine synthesis/Unknown	[24]
TLE1	9	1.07	0.57	MA, CC	Transcriptional corepressor/Unknown	[26,27]
TP53INP1	8	1.06-1.11	0.48	MA	Proapoptotic protein/Unknown	[22]
TSPAN8	12	1.06-1.09	0.27-0.71	MA	Cell surface glycoprotein/β-cell function	[22-24]
LGR5					G-protein coupled receptor/β-cell function	
WFS1	4	1.10-1.13	0.60-0.73	GCS	Transmembrane protein/β-cell function	[22,24,54,55]
ZBED3	5	1.08-1.16	0.26	MA	Zinc finger/b-cell function	[22]

ZFAND6	15	1.01-1.11	0.60-0.72	MA	Zinc finger/β-cell function	[22,24]
ZMIZ1	10	1.08	0.52	MA, CC	Transcriptional regulator/Unknown	[26,27]
Haplogroup B	mtDNA	1.52	0.25	GCS		[56]
OriB	mtDNA	1.10	0.30	MA		[57]

Chr: Chromosome; MA: Meta-analysis; LA: Linkage analysis; GWAS: Genome-wide association study; GCS: Gene candidate study.

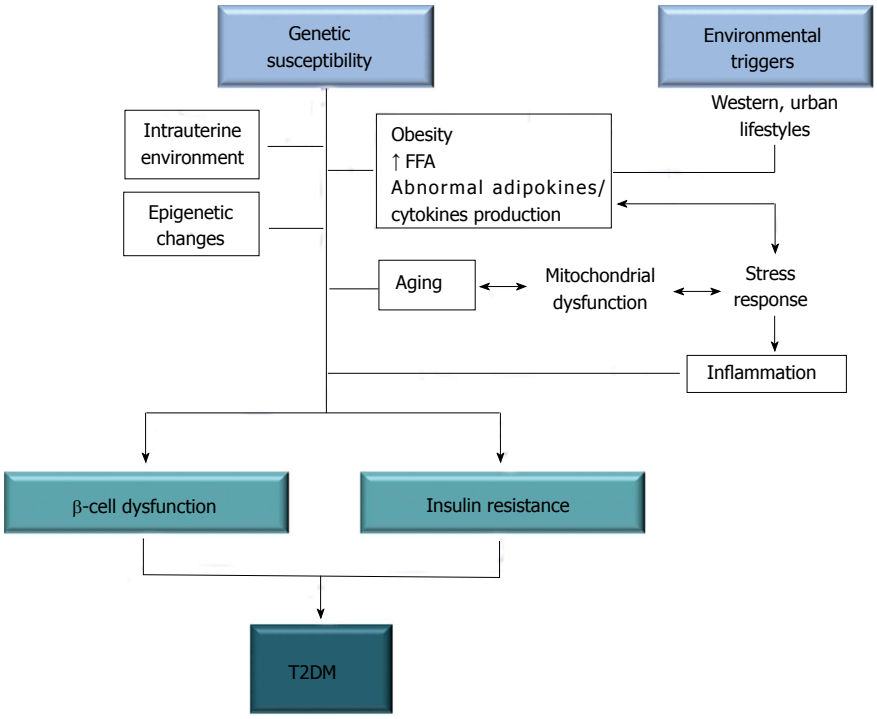

Figure 1 Overview of the pathogenic factors underlying development of type 2 diabetes mellitus. As a complex disease, T2DM is caused by a combination of genetic, environmental and lifestyle factors, all of which interact together to produce insulin resistance and β-cell dysfunction, leading to hyperglycemia, which is the clinical hallmark of diabetes. FFA: Free fatty acids. T2DM: Type 2 diabetes mellitus.

tion studies (GWAS), a technique commonly used to find links between genes and diseases across a substantial population. This strategy uses a database of over a million known genetic variants, which represent the majority of all common variants (minor allele frequency > 5%-10%), thus offering the possibility of simultaneously analyzing thousands of variations in a large number of patients and to perform meta-analysis of data from multiple studies. This methodology has helped to identify dozens of new associations between T2DM and genes with known or unknown functions (Table 1)[22-57], confirming some of the results from previous studies. However, despite the great potential of this approach, it is estimated that genetic variants identified through GWAS explain only 10% heritability for T2DM[58,59]. These relatively modest results can be explained taking into account some important limits of this strategy, such as the involvement of novel genetic variants not yet covered in the GWAS database, or the presence of variants with a frequency lower than the minimum threshold value. This means that the genes identified by GWAS so far are just the tip of the iceberg and that T2DM, far from being a condition limited to a few genetically and phenotypically prevalent forms, actually encompasses a heterogeneous group of genetically distinct disorders[18].

However, in many genetic studies carried out to date, the functional mechanism(s) by which the associated gene may increase susceptibility to T2DM is often poorly understood. In this respect, the intrinsic limitations of both the linkage analysis and GWAS are amplified by the fact that, in most cases, the genetic variants identified are located in non-coding regions of the DNA, whereby it becomes even more difficult to trace the role and influence of the associated gene in the development of the disease. In cases in which it was possible to ascertain the precise pathogenic mechanism, for example, through the study of association with the circulating levels of insulin or through the direct analysis of the gene's protein product, it has been seen that most of the genes identified are involved in pancreatic β-cell mass and/or function, thus with implications in insulin secretion defects (Table 1). This observation suggests that most of the risk associated with T2DM in the general population relates to genetic defects in β-cells, while peripheral insulin resistance predominantly suffers from the environmental component[18,19,60].

GENES INVOLVED IN β-CELL INSULIN SECRETION

Figure 2 depicts some of the genes whose alteration confers an elevated risk of T2DM. Using the analysis of functional or positional candidate genes, several variants have been identified, including polymorphisms of the gene insulin receptor substrate-1 (*IRS-1*)[22,24,43]. The Gly972Arg variant of IRS-1 determines a defect in the

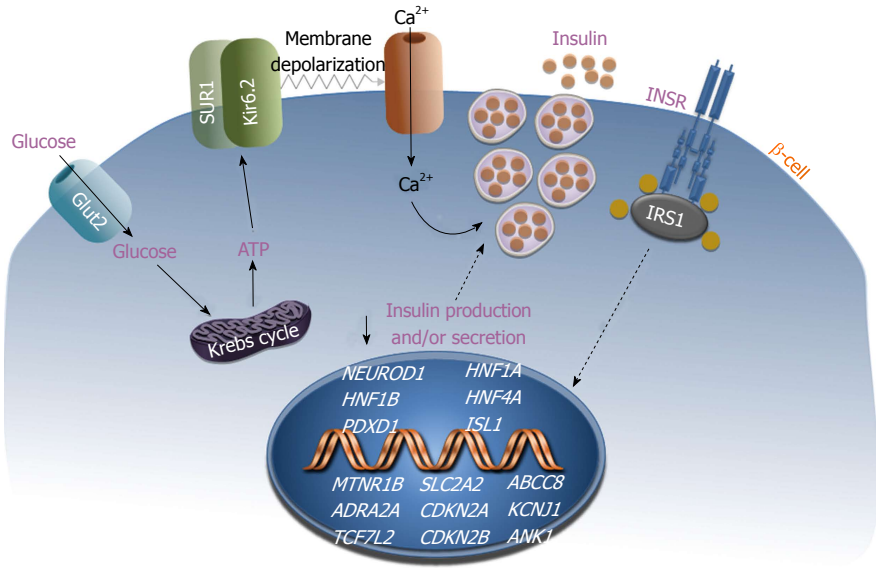

Figure 2 Schematic representation of the pancreatic β-cell. Reduced insulin secretion is shown in β-cells with gene variants linked to T2DM. Genes associated with defects in β-cell mass and/or function are indicated in white italic uppercase. T2DM: Type 2 diabetes mellitus.

binding of the p85 subunit of the phosphatidylinositol 3-kinase (PI3K) which in pancreatic β-cells causes a marked decrease in insulin secretion in response to glucose and sulfonylureas[61]. Other polymorphisms implicated in T2DM have been identified in the *ABCC8* (also known as *SUR1*) and *KCNJ11* genes, whose protein products take place in the formation of the Adenosine triphosphate (ATP)-sensitive potassium channel/sulfonylurea receptor of the pancreatic β-cell. The therapeutic response to sulfonylureas is compromised in patients with mutations in these genes. Other genes whose mutations were initially considered responsible for the less common forms of diabetes mellitus have subsequently been associated with an increased risk of T2DM[19]. Among these are the hepatocyte nuclear factor-1 homeobox A (A*HNF1A*) gene, whose mutations are responsible for the most common monogenic form of MODY (MODY3), a form of maturity onset diabetes of the young (also known as HNF1A-MODY), and the gene hepatocyte nuclear factor-1 homeobox B (*HNF1B*), which determines a less frequent but more severe monogenic form of diabetes, the MODY5. Both of these genes encode nuclear transcription factors involved in the development and function of pancreatic islets.

As already mentioned, the association between *TCF7L2* gene polymorphisms and susceptibility to T2DM was highlighted initially by linkage studies and confirmed thereafter by GWAS. However, only recently has the role played by the transcription factor TCF7L2 in the β-cell insulin secretion become evident[62]. Another gene that has recently been associated with T2DM is the melatonin receptor 1B (*MTNR1B*) gene which encodes for the receptor of the pineal hormone melatonin, MTNR1B, that is involved in the regulation and facilitation of sleep. Genetic variants of the *MTNR1B* gene, associated with gain-of-function of the MTNR1B receptor protein and a reduction in insulin secretion, have been reported in diabetic patients with abnormalities in melatonin secretion and circadian rhythm disorders of the sleep-wake cycle[63]. Another example of genetic abnormality associated with β-cell dysfunction and the risk of T2DM involves the *ADRA2A* gene that encodes for the alpha 2A-adrenergic receptor, which mediates the adrenergic suppression of insulin secretion[60]. Diabetic patients with polymorphisms of the *ADRA2A* gene may have overexpression of the alpha 2A receptor, resulting in insulin secretion deficiency. In pancreatic islets obtained from diabetic patients carrying this variant, pharmacological treatment with alpha (2A)-AR antagonists rescued insulin secretion[64].

Recently, large scale GWAS meta-analyses and imputation-based GWAS studies have demonstrated that the ankyrin 1 gene, a gene encoding for a protein of the ankyrin family, is associated with T2DM in different ethnicities[26-28]. Ankyrin 1 is typically expressed in the erythrocytes and functions as an adaptor molecule between membrane and skeleton proteins. Interestingly, mutations of this gene are known to determine hereditary spherocytosis. How this protein can be implicated in T2DM is not yet understood; however, ankyrin 1 is also expressed in β-cells, where a cognate protein, ankyrin B, plays a role in regulating ATP sensitivity by interacting with the sulphonylurea receptor isoform SUR1.

Another recent study has identified new loci and variants in a large-scale gene-centric meta-analysis that included the *SLC2A2* (solute carrier 2A2) gene[24]. This gene encodes the glucose transporter Glut2, which is expressed in pancreatic β-cells, liver and kidney, and functions as a glucose sensor to maintain glucose homeostasis. These findings support a previously postulated role of Glut2 in T2DM[65]. Also, variants of genes involved in the cell cycle, like the *CDKN2A* and *CDKN2B* (cyclin-dependent kinase inhibitor 2A and 2B) genes, have been associated with T2DM. Although not proved in humans, data from animal models support the idea that these genetic variants may affect β-cell mass later in life[66].

GENES INVOLVED IN INSULIN RESISTANCE

The first step in the mechanism of action of insulin is

the interaction of the hormone with its specific receptor, the insulin receptor (INSR), on the cell surface of insulin responsive cells and tissues (Figure 3). The functional activation of INSR is a key moment in the pathophysiology of insulin action, followed by the selective activation of specific intracellular signaling pathways which are necessary for proper hormonal signal transduction. Although defects in INSR have been reported in a large number of patients with T2DM, mutations in the *INSR* gene have been found only in a small percentage (3%-4%) of these patients in whom genetic defects leading to receptor protein abnormalities were identified as cause of disease. However, certain patients with apparently normal *INSR* genes have reduced expression of both the INSR protein and INSR mRNA levels[13,18,19]. In these patients, it is possible that there are mutations in genes encoding transacting factors which regulate the level of *INSR* gene expression[40].

The mechanisms by which gene variants may impair insulin action in insulin target tissues are schematized in Figure 3. Among the genes involved in insulin resistance are those encoding for the glucokinase regulatory protein, GKRP, and the insulin-like growth factor- I , IGF- I . Genetic variants of these genes that predispose a person to develop insulin resistance have been recently identified by GWAS[25]. In addition, T2DM risk alleles at three loci (at *FTO*, *KLF14* and *PPARG*) have been associated with higher fasting insulin (which is consistent with a primary defect on insulin action) and reduced insulin sensitivity[22]. In particular, variations in the fat mass and obesity-associated (*FTO*) gene appear to influence predisposition to T2DM through a positive effect on body mass index and obesity. Instead, the Krüppel-like factor 14 (*KLF14*) gene is considered a super gene with the ability to control other genes linked to body fat. The risk alleles at *KLF14*, along with those at peroxisome proliferator-activated receptor gamma (*PPARG*), appear to have a primary effect on insulin action which, unlike the alleles at *FTO,* is not driven by obesity[22].

A recently uncovered gene implicated in T2DM is the growth factor receptor-bound 14 (*GRB14*) gene[26,27], which codes for the Grb14 adaptor protein. Grb14 contains a C-terminal SH2 domain implicated in the interaction with a number of tyrosine kinase receptors and signaling proteins, and a domain called BPS (between pleckstrin homology), also required for binding to the INSR. This protein has been shown to specifically attenuate insulin action by inhibiting the catalytic activity of the INSR in insulin target tissues[67]. Many other recently identified diabetes-associated genes play still unknown roles in the pathophysiology of T2DM. Among them, the sterol regulatory element-binding transcription factor 1 (*SREBF1*) gene, which is involved in the transcriptional regulation of lipid homeostasis[24], and the high mobility group 20A (*HMG20A*) gene, which encodes a chromatin-associated protein and has previously been associated with a greater incidence of diabetes in obese subjects[26,27].

THE HIGH MOBILITY GROUP A1 GENE

Among the group of genes recently associated with insulin resistance and T2DM is the *HMGA1* gene, which encodes the architectural transcription factor, High Mobility Group A1 (HMGA1), a nonhistone basic protein that binds to AT-rich sequences of DNA *via* AT hooks, facilitating the assembly and stability of a multicomponent enhancer complex, the "enhanceosome", which drives gene transcription[68]. We previously found that HMGA1 is a key regulator of *INSR* gene expression[69-71] (Figure 4). Consistent with these findings, we identified two patients with insulin-resistant T2DM who had defects in HMGA1 expression and concomitant decreased INSR mRNA and protein in muscle, fat and circulating monocytes[72]. These individuals had normal *INSR* genes but had a novel genetic variant (*c.*369del*) in the 3' noncoding region of the HMGA1 mRNA that contributed to the reduction of mRNA half-life and subsequent decline in HMGA1 expression. Epstein-Barr virus (EBV)-transformed lymphoblasts from these patients demonstrated defects in HMGA1 and INSR expression, indicating that the defects observed *in vivo* were not due to the altered metabolic state of the patients. In addition, the *in vitro* restoration of HMGA1 RNA and protein expression in these cells normalized *INSR* gene expression and restored both cell-surface INSR protein expression and insulin binding capacity[72]. The pathogenetic role of HMGA1 in T2DM was confirmed in genetically modified mice, in which the loss of HMGA1 expression (induced by disrupting the *HMGA1* gene) considerably decreased INSR expression in the major target tissues of insulin action[72], thus supporting the concept that functional *HMGA1* gene variants decrease INSR expression in human and mice.

In the context of these investigations, we later showed that four functional variants of the *HMGA1* gene, leading to reduced INSR expression, were associated with insulin resistance and T2DM[40]. The most frequent functional *HMGA1* variant, c.136-14_136-13insC (also designated rs146052672), was detected in 7%-8% of patients with diabetes in individuals of white European ancestry[40]. Analysis of cultured EBV-transformed lymphoblasts from patients with T2DM and the rs146052672 variant revealed that these cells had lower levels of HMGA1 and INSR protein than cells from either patients with wild-type T2DM or controls. Once again, in transformed lymphoblasts from the patients with the *HMGA1* rs146052672 variant, restoration of HMGA1 protein expression by complementary DNA transfection (in the sense but not antisense direction) restored INSR protein expression and insulin binding to these cells[40]. Although not replicated in a heterogeneous French population[73], the *HMGA1* rs146052672 variant was significantly associated with T2DM among Chinese[41] and Hispanic-American[38] individuals. Further evidence, implicating the HMGA1 locus as one conferring a high cross-race risk for the development of insulin

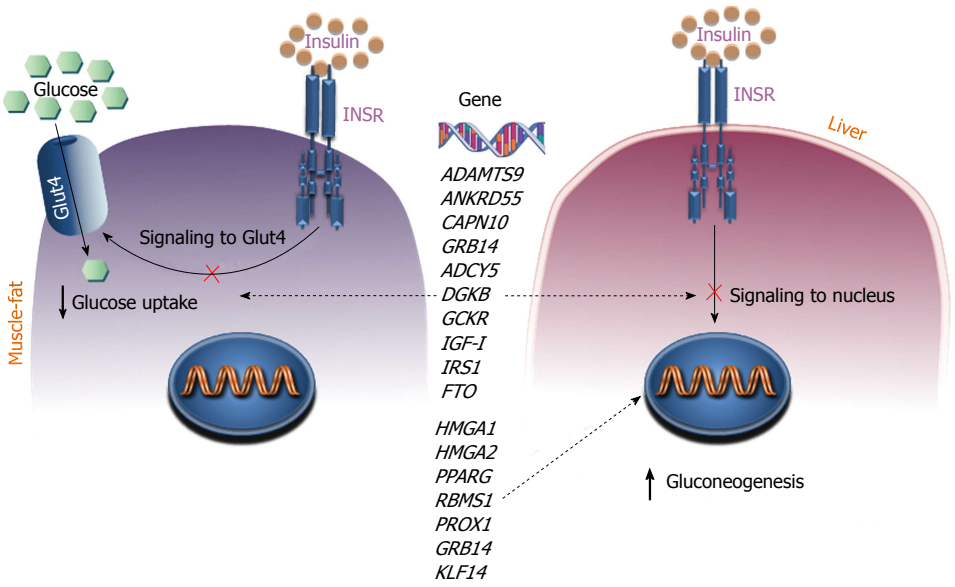

Figure 3 Mechanisms of insulin resistance. The figure shows the mechanisms by which gene variants may impair insulin action in the insulin target tissues muscle, fat and liver. Peripheral insulin resistance in muscle and fat reduces cellular glucose uptake, whereas insulin resistance in liver results in a failure to suppress glucose production and gluconeogenesis. Genes whose variations can influence the risk of developing insulin resistance and T2DM are indicated in black italic uppercase. T2DM: Type 2 diabetes mellitus.

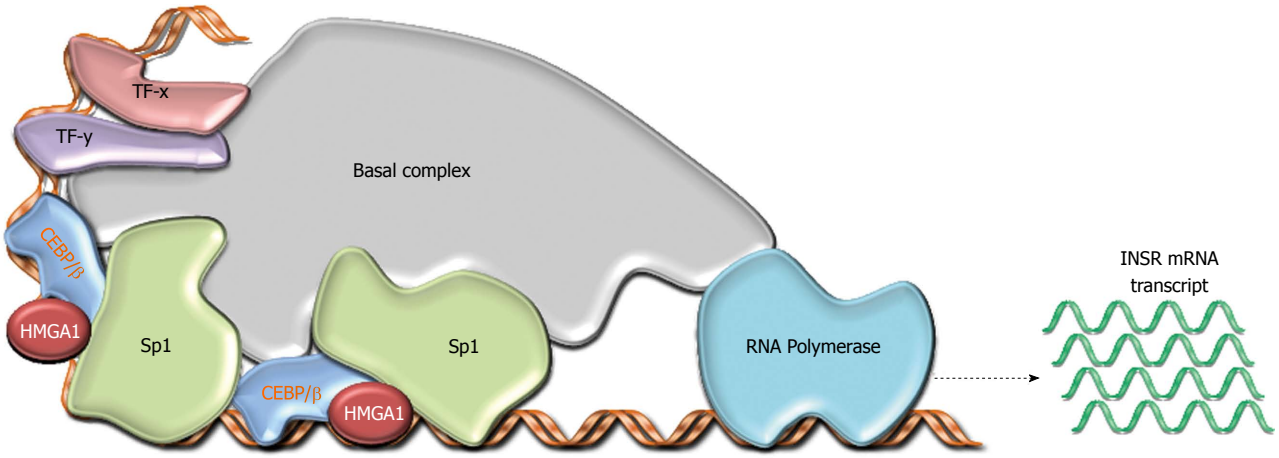

Figure 4 Model for the role of High Mobility Group A1 in type 2 diabetes mellitus. As a transcriptional regulator of the *INSR* gene, *HMGA1* gene variants may lead to decreased *INSR* gene transcription. This loss of insulin receptor (INSR) underlies the resultant insulin resistance and T2D in affected individuals. T2D: Type 2 diabetes.

resistant diseases, has been provided recently by showing that the *HMGA1* rs146052672 variant significantly associates with the metabolic syndrome in Italian and Turkish individuals and predisposes these (and other) populations to the unfavorable anthropometric and metabolic traits of the metabolic syndrome[74,42].

Overall, these data are consistent with the impression that the association of *HMGA1* gene variants with T2DM is accomplished through a pathogenetic mechanism related to peripheral insulin resistance. However, additional studies *in vitro* and *in vivo*, in normal and mutant mice, indicate that HMGA1, in addition to its role on *INSR* gene and protein expression, acts as a novel downstream target of the INSR signaling pathway[75], thus representing a critical nuclear mediator of insulin action and function. In this regard, evidence has been provided indicating that HMGA1 plays an essential role in the transcriptional regulation of a variety of insulin-target genes, such as the *IGFBP-1* gene, as well as the gluconeogenic genes *PEPCK* and *G6Pase*[76], contributing to the transcriptional regulation of glucose homeostasis.

PERSPECTIVES

Significant advances have been made in recent years in relation to the pathogenesis of T2DM. This has significantly improved our knowledge of one of the most serious health threats in the world, allowing identification of genes and pathways involved in the development and progression of the disease. It has recently become possible to acquire molecular and genetic level information from an individual (*i.e.*, DNA genotyping, gene expression, epigenomic profile, *etc.*). However, while such information is becoming increasingly available, how the identified genes and pathways impact on T2DM still remain largely unknown, due to the multifactorial nature of the disease. Understanding the pathogenesis of T2DM is necessary to enable the identification of prognostic and predictive biomarkers, as well as new therapeutic targets, which in turn should lead to improved outcomes in affected patients. Thus, once new therapeutic targets of

interest are identified, it is necessary to develop molecules that can rescue function to disease-associated genes or pathways and conduct studies that provide new strategies for the treatment of T2DM.

CONCLUSION

T2DM is a heterogeneous disease with a strong genetic component and familial inheritance. Considerable effort has been made in the last decades to identify genes that may explain all the diabetic phenotypes. Currently, however, genetic studies on T2DM can explain only a small percentage of its heritability. Until now, the *HMGA1* gene displays the strongest association with T2DM and its most frequent variant, rs146052672, confers the highest risk for human T2DM. Hence, from a strategic point of view, this finding suggests directing future research towards the identification of rare genetic variants with a stronger association, rather than common variants with a relatively small effect on the disease. It is evident that if a genetic variant confers a high susceptibility to T2DM it may become a useful biomarker to search for. For example, the genetic variants identified in the *HMGA1* gene may represent a predictive marker for early detection of T2DM, especially in those individuals with a family history of the disease. Moreover, variants in the human *HMGA1* gene may induce a different clinical course of disease compared to diabetic patients without the variant and may predict response to therapy, allowing identification of a priori patients who could most benefit from a specific pharmacological treatment[77]. Another important point in support of genetic studies in T2DM is the fact that they may integrate and improve our knowledge about the molecular mechanisms underpinning the pathophysiology of this disease.

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