Review Article

Genes predisposing to type 1 diabetes mellitus and pathophysiology: a narrative review

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ABSTRACT

The possibility of targeting the causal genes along with the mechanisms of pathogenically complex diseases has led to numerous studies on the genetic etiology of some diseases. In particular, studies have added more genes to the list of type 1 diabetes mellitus (T1DM) suspect genes, necessitating an update for the interest of all stakeholders. Therefore this review articulates T1DM suspect genes and their pathophysiology. Notable electronic databases, including Medline, Scopus, PubMed, and Google-Scholar were searched for relevant information. The search identified over 73 genes suspected in the pathogenesis of T1DM, with human leukocyte antigen, insulin gene, and cytotoxic T lymphocyte-associated antigen 4 accounting for most of the cases. Mutations in these genes, along with environmental factors, may produce a defective immune response in the pancreas, resulting in β-cell autoimmunity, insulin deficiency, and hyperglycemia. The mechanisms leading to these cellular reactions are gene-specific and, if targeted in diabetic individuals, may lead to improved treatment. Medical practitioners are advised to formulate treatment procedures that target these genes in patients with T1DM.

KEYWORDS autoimmunity, hyperglycemia, insulin, pancreas, type 1 diabetes mellitus

Diabetes mellitus (DM) begins when hyperglycemia occurs. A hormone synthesized by the pancreatic β-cells, known as insulin, regulates blood glucose by transporting it from the bloodstream into the cells where it is metabolized. Another hormone produced by the pancreatic α-cells, known as glucagon, also assists the body in the blood glucose regulation process. In most cases, type 1 diabetes mellitus (T1DM) occurs when the immune system, which normally attacks only foreign antigens, faultly destroys the β-cells. Consequently, the pancreas stops making insulin, leading to the retention of glucose in the blood.[1] Some people develop a condition known as secondary DM, which is like T1DM, but the immune system does not destroy the β-cells.[2] Instead, the cells are removed by certain stimuli in the pancreas, as indicated by histopathological changes.[2] T1DM was previously named juvenile DM but was renamed because adults can also develop the disease. Moreover, T1DM is not the only form of DM that affects children and young adults. Particularly, type 2 diabetes mellitus (T2DM) is becoming increasingly prevalent among young

individuals as more and more children are becoming obese and overweight nowadays.[3] Maturity-onset diabetes of the young and neonatal diabetes mellitus are other forms of DM that mainly affect children and neonates with different clinical features from T1DM.

T1DM is the most frequent chronic illness among children, accounting for 5–10% of all DM cases.[2] It is the most burdensome form of DM, with a decreased life expectancy.[4] About 30 million people live with T1DM worldwide, and the prevalence is predicted to increase three-fold in the 2040s.[5] Uncontrolled T1DM may cause chronic complications, including retinopathy, nephropathy, neuropathy, and vascular diseases. T1DM has a strong genetic etiology modulated by some environmental triggers that may prevent the disease if avoided before autoimmunity. The treatment involves constant insulin injections, which is expensive; thus, a better approach is necessary to stem the burden of the disease. As autoimmunity is the hallmark of T1DM, an intervention that re-programs the immune system may be a potential way to treat the disease. This observation suggests that precision medicine that targets causal genes and the pathophysiology of complicated diseases, such as DM, may provide a future management when fully understood. Hence, this review was initiated to search notable electronic databases, including Medline, Scopus, PubMed, and Google-Scholar to establish T1DM suspected genes. The result will facilitate the formulation of drugs and treatment procedures that target these genes and their mechanisms.

T1DM SUSPECT GENES

At least 18 regions in the human genome were identified as hotspots for T1DM using genome-wide linkage analysis. These regions host many genes and are labeled *IDDM1-IDDM18* because T1DM was formerly called insulin-dependent DM (IDDM).[6] However, improvement in biological techniques has led to a greater understanding of the genetic basis of T1DM. More precise studies have reaffirmed the roles of some previously suspected genes in T1DM pathogenesis and new ones have been discovered. Many genes have been reportedly linked with T1DM, but only those with clear mechanisms are presented in this review. Tables 1–3 show the update on T1DM candidate genes, grouped according to their mechanisms of action, which are disruption of T cell regulatory activities, increased susceptibility to microbial infection, oxidative stress, cytokine-induced β-cell loss, and β-cell reconfiguration. However, more genes are being added continually.

Most frequently suspected T1DM predisposing genes

Of the genes described in Tables 1–3, mutations in the major histocompatibility complex (MHC), insulin gene (*INS*), cytotoxic T lymphocyte-associated protein 4 (*CTLA4*), protein tyrosine phosphatase, non-receptor type 2 (*PTPN2*), and protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*) genes account for most of the T1DM cases. Detailed information on the diabetogenic activities of these genes is given below.

Table 1. T1DM suspect genes that disrupt T cell immune regulatory activities and increase susceptibility to microbial infection

Gene	Full name	Locus	Mechanism
CTLA4	Cytotoxic T-lymphocyte associated protein 4	2q33.2	Causes massive lymphocyte proliferation, resulting in overexpression of T cells, which attack self-antigens, leading to β-cell apoptosis.[7]
FOXP3	Forkhead box P3	Xp11.23	Disrupts the activities of many endocrine glands, affecting the immune regulatory T cells and setting of autoimmunity.[8]
PRKCQ	Protein kinase C theta	10p15.1	Loss of T cell signaling, leading to a compromised immune system.[9]
IL7R	Interleukin 7 receptor	5p13.2	Causes a compromised immune system, characterized by depletion of T cells.[10]
IL2	Interleukin 2	4q27	Causes functional loss of T cell (Treg) regulation, resulting in autoimmunity.[11]
ITGB7	Integrin subunit beta 7	12q13.13	It disrupts the activities of T cells in the pancreas, resulting in autoimmunity.[12]
SH2B3	SH2B adaptor protein 3	12q24.13	Increases self-reactive T lymphocyte proliferation.[13]
RASGRP1	RAS guanyl releasing protein 1	15q14	Reduced expression results in splenomegaly and autoantibodies, while complete deletion decreases T cell development in the thymus.[14]

Table 1. (continued)

Gene	Full name	Locus	Mechanism
CD28	CD28 molecule	2q33.2	Mediates loss of function of regulatory T cells, leading to autoimmunity of the pancreatic β-cells.[15]
ICOS	Inducible T cell costimulator	2q33.2	It suppresses insulin-specific regulatory T cells.[16]
ART2/RT6	Antisense to ribosomal RNA transcript protein 2	11p15.4	Causes insulitis in which the islets are massively infiltrated by macrophages and T cells.[17]
UBASH3A	Ubiquitin associated and SH3 domain containing A	21q22.3	Increases UBASH3A expression in CD4+ T cells, disrupting NF-κB signaling, which in turn represses *IL2* gene expression.[18]
SUMO4	Small ubiquitin-like modifier 4	6q25.1	Reduces sumoylation capacity, causing overexpression of NF-κB and IL12B, and leading to β-cell autoimmunity.[19]
MHC	Major histocompatibility complex	6p21.31	Causes loss of T cell signaling, leading to autoimmunity of the pancreatic β-cells.[20]
NRP1	Neuropilin 1	10p11.22	Causes defects in Treg phenotype decreasing its signaling activities, culminating in autoimmunity of the β-cells.[21]
MIF	Macrophage migration inhibitory factor	22q11.23	Causes high MIF concentrations in the blood, resulting in dysfunctional pancreatic islets. Also causes loss of function of immune cells, such as macrophages and T cells, increasing the risk of β-cell autoimmunity.[22]
CD226	Cluster of differentiation 226	18q22.2	Increases the frequency of GAD autoantibody and lowers C-peptide levels, accelerating β-cell destruction.[23]
IL6	Interleukin 6	7p15.3	Impairs immune response, leading to β-cell autoimmunity, it also leads to impaired fat breakdown in tissues such as muscle cells.[24]
IL10	Interleukin 10	1q32.1	It negatively regulates a T cell called Th17, setting up autoimmunity of the pancreatic β-cells.[25]
IL12B	Interleukin 12B	5q31-33	It negatively regulates a T cell called Th17, setting up autoimmunity of the pancreatic β-cells.[26]
PTPN22	Protein tyrosine phosphatase, non-receptor type 22	1p13.2	Disrupts elimination of autoreactive β-cells, and upregulates certain β-cell genes, leading to β-cell death.[27]
VDR	Vitamin D receptor	12q13.11	It causes dysfunctional immune mechanism, leading to autoimmunity.[28]
IL26	Interleukin 26	12q15	Disrupts sensing of bacteria by the defense mechanism,[29] resulting in the attack of β-cells.
TAGAP	T cell activation RhoGTPase activating protein	6q25.3	Causes deficiency of several important regulators of antiviral response, including IFN-β, culminating in loss of antiviral signaling pathways, and β-cell autoimmunity.[30]
TYK2	Tyrosine kinase 2	19p13.2	Represses TYK2, predisposing the body to virus attack.[31]
GAD2	Glutamic acid decarboxylase 2	10p12.1	Promotes invasion of β-cells by viruses, setting of autoimmunity of the β-cells, leading to insulin deficiency.[32]
OAS1	2'-5'-oligoadenylate synthetase 1	12q24.13	Predisposes to viral infection, setting in β-cell autoimmunity.[33]
IFIH1	Interferon induced with helicase C domain 1	2q24.2	Produces abnormal antiviral immune response, increasing the risk of autoimmunity.[34]
FUT2	Fucosyltransferase 2	19q13.33	Alters the gut microbiome, increasing the risk of autoimmunity of the β-cells.[35]

T1DM=type 1 diabetes mellitus; Treg=regulatory T cell; NF-κB=nuclear factor kappa B; Th17=T helper 17 cells; IFN-β=interferon beta

Table 2. T1DM suspect genes that mediate oxidative stress and cytokine-induced β-cell loss

Gene	Full name	Locus	Mechanism
SIRT1	Sirtuin 1	10q21.3	Produces defective sirtuin, inducing cytokines to attack wrong cells, particularly β-cells.[36]
ERBB3	Erb-B2 receptor tyrosine kinase 3	12q13.2	Disrupts antigen presentation, causing cytokine-induced β-cell apoptosis.[37]
PTPN2	Protein tyrosine phosphatase, non-receptor type 2	18p11.21	Produces cytokine, which induces destruction of β-cells and mitochondrial apoptotic pathway, disrupting glucose metabolism.[38]
BACH2	BTB domain and CNC homolog 2	6q15	Decreases *PTPN2* expression, promoting pro-inflammatory cytokine-induced β-cell apoptosis.[39]
IL21	Interleukin 21	4q27	Causes inflammatory infiltration of pancreatic islets.[40]
CENPW/C6orf173	Centromere protein W	6q22.32	Contributes to the generation of autoantibodies in the islets.[41]
AFF3	AF4/FMR2 family member 3	2q11.2	Alters the expression of monocytes as well as macrophages and dendritic cells, causing gradual destruction of β-cells.[42]
TNFAIP3	Tumor necrosis factor alpha induced protein 3	6q23.3	Loss of functional regulation of β-cell apoptosis, leading to poor glycemic control.[43]
RNLS	Renalase, FAD dependent amine oxidase	10q23.31	Alters the expression of monocytes as well as macrophages and dendritic cells, causing gradual destruction of β-cells.[44]
GPR183/EBI2	G protein-coupled receptor 183	13q32.3	Changes the expression of monocytes as well as macrophages and dendritic cells, causing gradual destruction of β-cells.[42]
CLECL1	C-type lectin like 1	12p13.31	Alters the expression of monocytes as well as macrophages and dendritic cells, causing gradual destruction of β-cells.[42]
DEXI	Dexamethasone-induced protein	16p13.13	Depletes gut microbial metabolites, causing autoimmunity of β-cells.[45]
SUOX	Sulfite oxidase	12q13.2	Alters the expression of monocytes as well as macrophages and dendritic cells, causing gradual destruction of β-cells.[42]
SMARCE1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily e, member 1	17q21.2	Alters the expression of monocytes as well as macrophages and dendritic cells, causing gradual destruction of β-cells.[42]
FKRP	Fukutin-related protein	19q13.32	Alters the expression of monocytes as well as macrophages and dendritic cells, causing gradual destruction of β-cells.[42]
IL27	Interleukin 27	16p11.2	Promotes inflammations of the islet cells.[46]
SOD2	Superoxide dismutase 2	6q25.3	Enhances generation of free oxygen radical, stressing, and contributing to β-cell death.[6]
BCL-2	B-cell leukemia/lymphoma 2	18q21.33	Initiates intracellular apoptotic pathway, resulting in islet cell death.[47]
FAS/CD95	Fas cell surface death receptor	10q23.31	Initiates glucose-induced DNA fragmentation, resulting in pancreatic islet apoptosis.[48]
IL-1A	Interleukin 1 alpha	2q14.1	Initiates glucose-induced DNA fragmentation, resulting in pancreatic islet apoptosis.[48]
APOC3	Apolipoprotein C3	11q23.3	Causes influx of Ca^{2+} into the β-cells, destroying the cells.[49]
BAD	BCL2-associated agonist of cell death	11q13.1	Loss of control of programmed cell death.[50]
NOS2	Nitric oxide synthase 2	17q11.2	Produces nitric oxide, inducing apoptosis in several cells, including β-cells.[51]

Table 2. (continued)

Gene	Full name	Locus	Mechanism
PTEN	Phosphatase and tensin homolog	10q23.31	Causes gradual destruction of β-cells.[52]
CASP7	Caspase 7	10q25.3	Causes gradual destruction of β-cells.[53]
HIP14	Huntingtin-interacting protein 14		Accelerates apoptotic cell death.[54]
STAT4	Signal transducer and activator of transcription 4	2q32.2	Its activation causes cytokine-induced islet apoptosis, resulting in β-cell dysfunction.[55]
CCR5	C-C chemokine receptor 5	3p21.31	Mediates infiltration of the pancreatic islets by abnormal blood cells, culminating in the gradual destruction of β-cells.[56]
ITPR3	Inositol 1,4,5-trisphosphate receptor type 3	6p21.31	Causes dysregulated calcium transport, leading to loss of insulin secretion function of the β-cells, culminating in high blood glucose and high HbA1c beyond healthy levels.[57]

T1DM=type 1 diabetes mellitus; HbA1c=hemoglobin A1c

Table 3. T1DM suspect genes that reconfigure β-cell morphology and identity

Gene	Full name	Locus	Mechanism
INS	Insulin gene	11p15.5	Breakage of phenylalanine amino acid, hampering maturation of preproinsulin to insulin.[58]
HNFIA	Hepatocyte nuclear factor-1 alpha	12q2431	Disruption of insulin biosynthesis, leading to hyperglycemia and osmotic diuresis.[59]
SLC2A2	Solute carrier family 2 member 2	3q26.2	Fanconi-Bickel syndrome, causing lack of insulin in utero.[60]
Amylin	Islet amyloid polypeptide	12p12.1	Causes over secretion of amylin, which aggregate in the pancreatic β-cells, causing β-cell death and impairing insulin secretion.[61]
NKX2.2	NK2 homeobox 2	20p11.22	Causes β-cell reconfiguration, leading to loss of insulin synthesis.[62]
GLIS3	GLI-similar 3	9p24.2	Suppresses insulin gene expression, causing pancreatic β-cell death.[63]
NEUROD1	Neuronal differentiation 1	2q32	Affects β-cell morphogenesis and differentiation, promoting β-cell apoptosis.[64]
CTSH	Cathepsin H	15q25.1	Progressively reduces the survival of β-cells.[65]
DLL1	Delta-like1- Drosophila	6q27	Hampers β-cell differentiation and maturation.[66]
ORMDL3 GSDMB	Orosomucoid like 3	17q12	Reduces sulfatide levels in the pancreatic islet, causing unregulated proinsulin folding as well as apoptosis.[67]
FADD	Fas-associated death domain	11q13.3	Disrupts transcription of pancreatic cells.[6]
CDKN1B/p27KIP1	Cyclin-dependent kinase inhibitor 1B	12p13.1	Causes loss of β-cell mass, and poor glucose metabolism.[68]
IRS2	Insulin receptor substrate 2	13q34	Reduces β-cell mass.[69]
IL2RA/CD25	Interleukin 2 receptor alpha	10p15.1	Causes inflammatory bowel disease, β-cell enlargement, leading to autoimmunity.[70]

T1DM=type 1 diabetes mellitus

MHC

MHC is about a 4 megabases genetic section on chromosome 6 (6p21) containing immune recognition genes.[20] Many versions of MHC occur among animal species.[20] In humans, it is called the HLA complex and contains over 200 genes grouped into class I, II, and III.[20] Class I has three major genes, named HLA-A, HLA-B, and HLA-C.[71] The proteins encoded by these genes are expressed on the surface of most nucleated cells, where they bind to protein fragments (peptides) exported from within the cell.[71] Class I proteins present these peptides to the immune system, and apoptosis is induced if the peptides are recognized as foreign, such as viral or bacterial peptides.[71] Human MHC class II has six main genes, including HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, and HLA-DRB1.[71] The proteins produced by these genes are expressed mainly on the surface of certain immune system cells, including B lymphocytes, dendritic cells, macrophages, and activated T lymphocytes.[71] Class II proteins display peptides to the immune system.[71]

HLA class I and II genes are highly polymorphic, and inheritance of certain variants may predispose the affected individual to an autoimmune disorder. Certain HLA class II alleles or combinations of alleles (haplotypes) significantly increase the risk of T1DM, while others confer reduced or protective effects.[72] For example, most individuals with T1DM are carriers of either HLA-DR3, DQB1*0201 (also called DR3-DQ2), or DR4-DQB1*0302 (otherwise known as DR4-DQ8).[72] Also, inheriting the HLA haplotype DRB1*0302-DQA1*0301, particularly when combined with DRB1*0201-DQA1*0501, increases genetic predisposition to T1DM as much as 20-fold.[72] In contrast, the haplotype DRB1*0602-DQA1*0102 rarely predisposes to T1DM,[72] while the haplotype HLA-DQ6 (HLA-DQA1*0102-DQB1*0602) is protective.[6]

INS gene

INS gene was the second gene linked with T1DM and accounts for about 10% of T1DM cases.[34] It encodes the precursor to insulin, which assists the body to store energy for later use.[73] For example, insulin helps the body store glucose as glycogen or fat rather than metabolizing it. Insulin has two separate polypeptide chains, chains A and B, and are connected by disulfide bonds.[73] Unlike some proteins that are synthesized by several genes, insulin is synthesized by the *INS* gene only. Some animals, such as rats and mice, have two insulin genes but humans only have one. To produce insulin, the *INS* gene secretes an inactive insulin precursor called preproinsulin, which is converted to another inactive substance called proinsulin by removal of a signaling peptide.[73] Insulin is finally produced from proinsulin by removal of the C-peptide that binds chains A and B together.[73] However, mutations in the *INS* gene may disrupt the insulin biosynthetic network, causing some diseases. A point mutation in the *INS* gene known as C96Y synthesizes mutant proinsulin, resulting in endoplasmic reticulum (ER) stress, which progressively causes death of β-cells and T1DM.[74] Several other point mutations have also been reported in individuals and animals with T1DM.

The promoter region of the *INS* gene is highly polymorphic and contains several variable numbers of tandem repeats (VNTRs), grouped into classes I, II, and III.[20] VNTR I contains 26–63 repeats, VNTR II has 80 repeats, and VNTR III has 140–210 repeats. Among Caucasians, VNTR I is highly prevalent, VNTR III is moderately prevalent, while VNTR II is rare. VNTR I homozygotes often develop T1DM than VNTR III, while VNTR II confers a protective effect.[20] A polymorphism in the promoter region of the *INS* gene determines the regulatory activities of the transcription factor autoimmune regulator on thymic expression of insulin. The VNTR I allele reduces tolerance to insulin and its precursors, repressing insulin transcription and predisposing the individual to T1DM.[20] The VNTR II allele promotes the expression of insulin mRNA in the thymus.[20]

CTLA4 gene

CTLA4 gene is expressed on the surface of activated T cells, where it attenuates the immune response by binding to ligands CD80 or CD86 expressed on the surface of antigen-presenting cells.[75] The CTLA4-CD80/CD86 complex represses the IL-2 receptor (CD25), reducing IL-2 synthesis or triggering cell death in already activated cells.[75] CTLA4 protein also mediates the suppressive activity of CD4+ CD25+ T regulatory cells.[75] The expression of *CTLA4* in activated T lymphocytes shows that it maintains immune function by preventing the inflammatory response and autoimmunity.[74] Thus, *CTLA4* plays a negative regulatory role in immune function by preventing the overexpression of T cells. Functional impairment in the *CTLA4* gene may cause overexpression of T cells, causing it to attack self-antigens. Deletion of the

CTLA4 gene in mice leads to massive proliferation of lymphocytes, resulting in autoimmunity and death.[74]

Several autoimmune disorders have been associated with functional loss or impairment of the *CTLA4* gene. A single nucleotide polymorphism (SNP) +6230G>A characterized by splicing of the gene or altered mRNA is linked with an increased risk for T1DM.[75] The promoter region of the *CTLA4* gene is polymorphic and a particular SNP –319C>T, which reduces the transcription of the gene, is related to a high risk of T1DM.[75] SNP involving an A-to-G substitution at nucleotide 49 in exon 1 (G49A), causing an amino acid substitution (Thr17Ala) has also been reported in patients with T1DM.[75] The predisposing Ala17 allele is partially glycosylated in the ER, resulting in retrograde transport of some molecules into the cytoplasm for lysis,[75] leading to less *CTLA4* (Ala17) at the cell surface, which may be responsible for loss of function of the *CTLA4* gene expressed by individuals with the +49G allele.[75] Thus, the G49A allele reduces the negative regulatory role of *CTLA4* and predisposes to TIDM, compared with the 49 G/G alleles, which confers protection.[74]

PTPN22 and *PTPN2* genes

PTPN22 and *PTPN2* genes both code for protein tyrosine phosphatase (PTP) signaling molecules that modulate and regulate several biological processes, including cell growth, survival, and differentiation.[76] PTPs are important regulators of signaling transduction, as they relay signals from the cell into the nucleus.[76] Besides cell growth and differentiation, these molecules initiate cell signaling for T cell immune regulatory activities.[76] PTPs are so important in immune regulation that they are more expressed on immune cells than other body tissues.[76] A deficiency of PTP in mice distinctively upregulates immune status with severe abnormalities in hematopoiesis, suggesting that PTPs play an important role in maintaining a balanced immune system.[76] A deficiency in these signaling molecules because of inactivation or loss of *PTPN2* or *PTPN22* leads to decreased suppression of the inflammatory response resulting from reduced negative regulation.[76]

PTPN22 is the fourth gene linked with T1DM in which the rs2476601 SNP disrupts PTP intracellular signaling, leading to loss of negative immune regulation.[75] The SNP causes a single substitution of arginine for tryptophan in the encoded protein (R620W), leading to

a decrease in T cell and B cell receptor signaling.[77] This may disrupt tolerance in both T and B cells, ultimately resulting in diabetes-specific autoimmunity.[77] The autoimmunity induced by this SNP is characterized by a preponderance of autoreactive B cells and autoantibodies, both of which are biomarkers for the onset and progression of T1DM.[77] The mechanism for the role of the *PTPN2* gene in the pathogenesis of T1DM is complex, consequent to expression in many cells, but is suspected to involve destruction of pancreatic β-cells. Functional loss of the *PTPN2* gene may also hamper negative regulation of the apoptotic pathway, leading to overexpression of T cells. Repression of the *PTPN2* gene impairs insulin production by β-cells in diabetic mice. In normal individuals, *PTPN2* gene blocks insulin signaling by dephosphorylation of its β-chain receptor with the assistance of PTP1B phosphatase. This, in turn, controls gluconeogenesis in the liver by suppressing STAT3 signaling and decreasing glucose production. Mutant *PTPN2* induces mitochondrial apoptotic pathways, resulting in β-cell apoptosis and unbalanced glucose metabolism. A version of *PTPN2* (rs1893217) has been reported to upregulate T cell receptor signaling in mice, causing impaired self-antigen recognition and β-cells destruction consequent to the loss of negative regulation.[38]

Application of autoantibodies and proteins of T1DM suspect genes as biomarkers

No guidelines have been established for T1DM genetic testing as it is done in DM with monogenetic etiology. This is partly because several genes may interact to cause T1DM and testing for individual genes may not be cost-effective. Also, genetic susceptibility alone may not fully explain the etiology of the disease as environmental triggers, such as diet, infection, and pollutants may play a role in onset of the disease. Nevertheless, the Immunology of Diabetes Society has suggested that certain autoantibodies in individuals with a family history of T1DN may predict the likelihood of the disease. These autoantibodies include islet cell antibodies, insulin autoantibodies, the GAD autoantibody, and the protein tyrosine phosphatase IA-2/ICA512.[78] Tables 1 and 2 present some genes that produce these autoantibodies. The β-cell function determined by the first-phase insulin response in the intravenous glucose tolerance test can also predict onset of the disease.[78] The genes whose mutations or variants affect β-cell differentiation and

morphology, resulting in loss or reduced functions, are shown in Table 3. The levels of the proteins produced by genes predisposing to enteroviruses, such as B coxsackieviruses, are also a good biomarker of the disease. Notable among these genes are the HLA, *PPTN22*, *PPTN2*, and *CTLA4* genes discussed earlier. Abnormal levels of the MHC and CTLA4 proteins could indicate enteroviral induced autoimmunity in T1DM, prompting a therapeutic measure. Viral infection may also raise the concentration of interferons in islet β-cells, which overexpress MHC I, resulting in increased susceptibility to cytotoxic CD8+ T cell recognition and destruction.[79] Other genes listed earlier whose concentrations are sensitive to viral infections include *ERBB3*, *PRKCQ*, *IL7R*, *IL2*, *TAGAP*, *IL26*, *IL10*, *IL12B*, and *OAS1* (Table 1).

In summary, the reviewed articles indicate that mutations in or variants of certain genes may induce autoimmunity in β-cells by compromising the immune system, predispose the carrier to T1DM. Many T1DM predisposing genes have been identified; however, individual genes alone cannot cause the disease. These genes interact with each other, suppressing or overexpressing the functions of one another and may induce DM along with environmental stimuli. These genes initiate DM through different mechanisms, which may result in improved treatment. Healthcare providers are advised to formulate treatment plans that target these genes and mechanisms rather than the current generalized treatment procedure.

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