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Genetic and Epigenetic Etiologies of Type 1 Diabetes Mellitus

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Abstract

Numerous suspect genes associated with type 1 diabetes mellitus (T1DM) have been identified, suggesting a need to focus on the disease's causal genes and mechanisms. This necessitates an update to raise public awareness. This review articulates genes with mutations that predispose individuals to T1DM. We conducted a comprehensive search of academic databases, including Web of Science, Scopus, PubMed, and Google Scholar, for relevant materials. Available information indicates that at least 70 genes are suspected in the pathogenesis of T1DM. However, the most frequently implicated genes include human leukocyte antigen (*HLA*), insulin (*INS*), cytotoxic T lymphocyte-associated antigen 4 (*CTLA-4*), and protein tyrosine phosphatase non-receptor type 22 (*PTPN22*). Mutations or variants in these genes may lead to insulin insufficiency and, consequently, T1DM by tricking immune cells, such as T-cells and B-cells, into attacking self-antigens and triggering the autoimmunity of beta cells. Furthermore, this pathophysiology can be mediated through aberrant epigenetic modifications, including DNA methylation, histone post-translational modifications, and non-coding RNAs, in the mentioned genes. Some of these pathophysiologies are gene-specific and may have an epigenetic origin that is reversible. In the event of an epigenetic origin, a treatment for T1DM that addresses the causal genes or reverses epigenetic changes and their mechanisms could yield improved outcomes. Medical professionals are encouraged to design therapeutic regimens that specifically target the mentioned genes and address the identified epigenetic alterations in individuals expressing such etiologies.

Keywords: Beta cells, DNA methylation, Epigenetics, Human leukocyte antigen, T-cells, Type 1 diabetes mellitus

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Introduction

The term "diabetes" refers to a syndrome including a range of metabolic disorders, elevated blood glucose levels (1). In individuals without diabetes, insulin, produced by pancreatic β-cells, and glucagon, produced by pancreatic α-cells, work together to regulate blood glucose concentrations (2). When glucose levels are low, glucagon stimulates the liver to break down glycogen into glucose, which is then released into the bloodstream. This process, known as glycolysis, raises blood glucose levels through catabolism, while insulin promotes anabolism to lower blood glucose levels (3). Type 1 diabetes mellitus (T1DM) often arises when the immune system erroneously attacks and destroys pancreatic β-cells, leading to insulin deficiency and hyperglycemia. It can also occur through non-immune mechanisms, triggered by certain environmental factors that damage and eliminate β-cells (4-6).

T1DM is the most prevalent chronic disease among children, affecting approximately 1.2 million children and adolescents aged 0 to 19 (7,8). Globally, over 9 million individuals live with T1DM, constituting about 10% of all diabetes cases, with 2.6 million individuals (29%) residing in developing nations (9). T1DM poses a significant burden and can shorten life expectancy (10), with mortality rates 3-18 times higher than those of the general population worldwide (11-13). While T1DM has a strong genetic component, environmental factors such as microbial infections, lifestyle choices, chemical exposures, and dietary habits have also been implicated in its pathogenesis (14-16). Studies have demonstrated a pair-wise concordance of T1DM ranging from 23 to 61% among monozygotic twins, highlighting additional risk factors beyond genetics (17). Furthermore, T1DM diagnosis sometimes coincides with or follows a viral infection, particularly during the winter months when the infections are more prevalent (18). The recent research has linked intrauterine epigenetic reprogramming to the development of T1DM, altering the expression of several genes involved in insulin production and glucose metabolism (19). However, there remains a lack of awareness regarding the role of epigenetic mechanisms in T1DM pathogenesis. The objectives of this study are to update the genetic foundations of T1DM and to shed light the role of epigenetic modifications in its development, along with potential strategies for reversal or prevention.

Genetic etiology of type 1 diabetes mellitus

At least 70 genes are linked to the onset of T1DM, with human leukocyte antigen (*HLA*), insulin (*INS*), cytotoxic T lymphocyte-associated antigen 4 (*CTLA-4*), and protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) genes accounting for most of the cases (2). The loss of function of these genes due to mutations, combined with environmental factors, can result in a false immune response, leading to pancreatic β-cell autoimmunity, insulin insufficiency, and hyperglycemia. These biological events are gene-specific, and if they are targeted in people with diabetes, it can result in better treatment.

1. The role of the human leukocyte antigen (*HLA*) gene in the etiology of type 1 diabetes

HLA genes are a family of genes with a 4 mega-base genetic region on chromosome 6 (p-21.3) (2). These genes produce several individual proteins that are called *HLA* complexes combined. They were named leukocyte antigens because they were seen for the first time on the surface of white blood cells (20). The human form of the major histocompatibility complex (MHC), which is found in many animal species, is the *HLA* system (21). Both parents contribute to the *HLA* gene pool in individuals; hence, they are polymorphic and therefore vary widely among individuals (22). The *HLA* gene polymorphisms result in varied tissue types

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among individuals and, as such, determine the compatibility of a donor and recipient during organ transplantation (23). Furthermore, the *HLA* complex regulates the immune response against disease. Due to the polymorphisms in *HLA* genes, people react differently to infections or diseases; some people may exhibit a more severe form of an infection or condition than others (23). This implies that some variants of *HLA* genes are protective, while some predispose humans to diseases. *HLA* gene variations have been linked to more than 100 diseases, including the human immunodeficiency virus, cancer, and autoimmune diseases such as DM and multiple sclerosis (23).

The *HLA* complex contains more than 200 genes grouped into Classes I, II, and III, each with a specific role (2). In increasing an immune response, *HLA* Class I genes, corresponding to *MHC* Class I (named A, B, and C genes), present peptides from inside the cell. When a virus invades a cell, the *HLA* Class 1 group, for example, transports viral peptides to the cell surface. This attracts T-lymphocytes (immune cells) named killer T-cells (also referred to as CD8+ or cytotoxic T-cells) and destroys the cells. *HLA* Class II (*DP*, *DM*, *DO*, *DQ*, and *DR* genes), which is the same as *MHC* Class II, presents antigens from the exterior of the cell to T-lymphocytes known as T-helper cells (also referred to as CD4+ T cells). This causes B-cells to secrete antibodies against that particular antigen. Self-antigens are inhibited by regulatory T cells in all of these cases. *HLA* Class III genes, corresponding to *MHC* Class III, are located in a chromosomal region between *HLA* Class I and Class II antigens (22). They do not have any classic *HLA* genes, but they do have some genes that are important for the immune system (22).

In non-diabetics, when *HLA* Class I genes present endogenous antigens or Class II genes present exogenous antigens to T cells, a tri-molecular complex (HLA-peptide-TCR) is created to initiate an immune response (20). In the complex, HLA stands for molecules initiated by class 1 or 2 (CD4+ or CD8+, respectively), the peptide represents the antigenic peptide, and TCR stands for T-cell receptor (24). However, in people with T1DM, the predisposing variant (s) does not produce the normal shape of the complex, causing a wrong immune response and autoimmunity in which CD4+ and CD8+ attack self-cells (22). Furthermore, the amino acid makeup of Class II genes' alpha- and beta-chains, one or more of which is deleted in the predisposing variant, determines their specificity to present antigens (25). The loss of one or more amino acids produces a defective immune response, leading to autoimmunity. The pancreas of people with T1DM is filled with CD4+ and CD8+ T cells, as well as macrophages, which attack and kill beta cells (26).

Variants of *HLA* genes account for about 40 to 50% of T1DM cases, of which polymorphisms in *HLA* Class II genes encoding *DQ*, *DR*, and *DP* account for the majority (20). The HLA-B class I gene alleles are also significantly linked to the condition. Two *HLA* alleles or haplotypes, *DR4-DQ8* and *DR3-DQ2*, are of particular interest as they have been implicated in 90% of children expressing T1DM (26). Another haplotype, *DR15-DQ6*, is protective and found only in about 1% of children with diabetes (26). Individuals that are homozygous for the two predisposing haplotypes (*DR4-DQ8*/*DR3-DQ2*) have the highest risk and express T1DM very early in life (26). Regarding *HLA* Class III, it contains genes whose loss of function or overexpression may lead to T1DM. These genes include, among other things, factor B (*BF*), complement component 2 (C2), steroid 21-hydroxylase (*CYP21*), and tumor necrosis factor (*TNF*) (27).

2. The role of insulin (*INS*) gene in the etiology of type 1 diabetes

The *INS* gene was the second gene discovered in the search for the genetic etiology of T1DM and accounts for approximately 10% of the genetic predispositions to T1DM (2). The *INS* gene is

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embedded on chromosome 11 and codes for insulin precursors (2). Insulin distributes glucose to the cells that need it, controlling blood sugar concentrations and assisting the body in storing energy as glycogen or fat for later use when the body is low on energy. The *INS* gene secretes preproinsulin, an inactive insulin precursor, which is then transformed into proinsulin, another inert molecule, and eventually into insulin (2). Mutations in the *INS* gene, however, can affect insulin biosynthesis, resulting in a variety of illnesses. For instance, a point mutation in the *INS* gene named *C96Y* causes mutant proinsulin to be synthesized, causing endoplasmic reticulum (ER) stress and eventually beta-cell death and T1DM. In people and animals with T1DM, several other point mutations in the *INS* gene have been discovered.

Polymorphisms in the *INS* gene promoter, located in the gene's upstream, also predispose to T1DM. This polymorphic site contains a variable number of tandem repeats (VNTRs), classed into three. Class I has 26-63 repeats, Class II has 80 repeats, and Class III has 140-243 repeats (25). Class III is found in about 30% of the general population and protects against T1DM regardless of *HLA* haplotypes (25). However, Class 1, with short VNTRs, is associated with susceptibility to T1DM (26). Individuals with long VNTRs have been found to have higher insulin mRNA expression in their thymus and effective deletion of insulin-specific T lymphocytes during central tolerance induction (26). This suggests that the types of inherited alleles in the *INS* gene's promoter region determine the thymic immune response during insulin production. The Class I allele reduces the person's tolerance to insulin and its precursors, which stops insulin transcription and increases the risk of T1DM (2). The Class II and III alleles, on the other hand, increase the expression of insulin mRNA in the thymus (2).

3. The role of the CTLA-4 (cytotoxic T lymphocyte associated-4) gene in the etiology of type 1 diabetes

CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) is a protein receptor that modulates immunological responses. It is otherwise called CD152 (cluster of differentiation 152) (28-29). This gene belongs to the immunoglobulin superfamily and codes for a protein that sends an inhibitory signal to T lymphocytes (30). It is found on chromosome 2's long arm (2q33.2). *CTLA-4* is always present in regulatory T cells but only up-regulated in activated T cells (29). The up-regulation of the *CTLA4* gene exclusively on the surface of activated T cells indicates that it maintains immunological function by preventing inflammation and autoimmunity (2). A study conducted by Lee et al. (31) shows that *CTLA-4* regulates immune response by recruiting a phosphatase to the T cell receptor (TCR), thus attenuating immune response signals. However, studies by Qureshi et al. (32) and Syn et al. (29) suggest that *CTLA-4* regulates immune function by binding with CD80 and CD86 to form a CTLA4-CD80/CD86 complex on the membranes of antigen-presenting cells, thus making these ligands unavailable for triggering immune response through CD28 (Cluster of Differentiation 28) and other molecules. CD28 is a CD80 and CD86 receptor that, along with the T-cell receptor (TCR) and other molecules, sends out strong signals that allow T cells to activate and produce numerous interleukins (e.g., IL-2 and IL-6). So, in healthy individuals, the CTLA4-CD80/CD86 complex suppresses interleukin receptors such as CD25 (IL-2 receptor), decreasing interleukin synthesis and causing apoptosis in activated cells (2). *CTLA4* inhibits T cell overexpression and thus plays a negative regulatory role in immune activity (2).

It then follows that the loss of function of the *CTLA4* gene may overexpress the T cells, causing them to attack self-antigens (2). In mice, deletion of the *CTLA4* gene causes enormous lymphocyte proliferation, culminating in autoimmunity and death (33). A single nucleotide polymorphism in the gene (called +6230G>A), which causes splicing or

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altered mRNA, has been related to a higher incidence of T1DM (34). Similarly, the -319C > T single nucleotide polymorphism in the promoter region of the *CTLA4* gene decreases the gene's transcription and consequently predisposes to T1DM (34).

4. The role of Protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) in the etiology of type 1 diabetes

The protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) gene resides on chromosome 1 (1 p13.3-p13.1) and codes for lymphoid-specific tyrosine phosphatase (LYP), an inhibitor of T cell activation (35). This protein regulates several biological activities, including cell proliferation, survival, and differentiation, as well as signal transduction (36). The *PTPN22* protein initiates cell communication for T cell immunity regulation and is so critical in immune regulation that it is expressed more on immune cells than on other human tissues (36). In a mouse experiment, LYP deficiency distinctively up-regulates immune responses, causing severe abnormalities in hematopoiesis, suggesting a role for LYP in immune maintenance (36). Loss of function of *PTPN22* has been shown to produce abnormal inflammatory responses resulting from reduced negative regulation (36).

A *PTPN22* polymorphism known as *C1858T* made *PTPN22* the fourth gene to be associated with T1DM (26). The mutation is a cytosine to thymine substitution that results in an arginine to tryptophan alteration at codon 620 of LYP, predisposing to T1DM. The mutation disrupts the immune-regulating signaling of LYP and that of C-terminal Src kinase (CSK), leading to uncontrolled TCR signaling and abnormally prolonged activation of T lymphocytes, which causes and perpetuates autoimmunity (35). This mutation reduces T cell receptor and B cell receptor signaling, disrupting the normal immune response from both T cells and B cells (37-38). The mutation in B cells inhibits auto-reactive B cells from being removed (37-38). As a result, autoimmunity caused by this variant is characterized by a high prevalence of auto-reactive B cells and autoantibodies, both of which are indicators of T1DM initiation and progression (2). The variant also causes up-regulation of genes that code for proteins that promote B cell activation, such as *CD40*, *TRAF1*, and *IRF5* genes (37).

Epigenetic etiology of type 1 diabetes mellitus

Heritable genetic and non-genetic variables that govern phenotypic presentations are called epigenetics. Epigenetic changes are like switches that can activate or deactivate genes, changing their function or expression, all without actually modifying the genetic code itself (39). Epigenetics can also be described as the molecular link that connects the genetic and environmental factors that control several biological processes in the body, including disease etiology (40). While DNA has complete control over the body, the epigenome modifies DNA or, more accurately, has complete control over its expression (40). Normal cellular functions, including growth and development, rely on epigenetic mechanisms. However, modification of the expression of genes that would normally protect people from certain diseases could make them more vulnerable to them (39). DNA methylation, histone post-translational changes, and noncoding RNA-mediated gene silencing are the most common epigenetic processes. Some research findings reveal that epigenetic pathways play a role in T1DM pathogenesis.

1. The role of DNA-methylation in the etiology of type 1 diabetes

DNA methylation is the covalent bonding of a methyl group to the fifth carbon of cytosine at a CpG site, creating a 5-methylcytosine (40). CpG sites are DNA sequences in which a cytosine nucleotide is followed in a linear order by a guanine nucleotide. CpG sites are found in abundance in genomic areas known as "CpG islands". Accurate DNA methylation is recognized to be vital in maintaining normal

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embryonic development, genomic imprinting, X-inactivation, and aging suppression, among other things (41). Abnormal DNA-methylation that disrupts the normal expression of certain genes is known to predispose to T1DM. The *HLA* genes, as well as the other immune-regulating genes and molecules discussed earlier, are among these genes. Abnormal DNA methylation of genes involved in beta cell development, maturation, and differentiation as well as insulin synthesis can also predispose to T1DM (42).

Moreover, DNA methyltransferase 3A (DNMT3A), one of the enzymes that catalyzes DNA methylation, is necessary for beta cell programming for insulin secretion after birth (43). This shows that abnormal DNA methylation may malfunction the pancreas and beta cells and thus predispose to T1DM. The CpG sites enhance *INS* transcription, but hyper-methylation of the sites, resulting in transcription repression, predisposes to DM (41).

Additionally, certain environmental triggers can cause overexpression of specific cytokines in the islets, resulting in hyper-methylation of DNMTs and *INS* gene and repressing insulin transcription (43). In addition, epigenetic regulations are also necessary for beta cell differentiation and identity maintenance, in which abnormal DNA methylation can cause loss of beta cell identity and predispose to T1DM. According to Moin and Butler (44), in order to prevent β - to α -trans-differentiation, the cell-specific DNA-binding protein Arx must be suppressed. Arx repression in β -cells is carried out partly by the binding of the transcription factor Nkx2.2 to the Arx promoter, followed by recruitment of DNMT3 and increased DNA (CpG) methylation.

A DNA-binding protein known as MeCP2 then binds to the promoter region of Arx in β -cells to initiate and maintain a perfect repressed state. So, epigenetic dysregulation involving abnormal DNA methylation may predispose to T1DM.

2. The role of histone post-translational modifications in the etiology of type 1 diabetes

Histones are spools of DNA that aid in its packaging into chromosomes (39). Histones are formed from a protein called chromatin. There are five main classes of histones, namely H1/H5, H2A, H2B, H3, and H4, but the core histones are histones H2A, H2B, H3, and H4, while the linker histone is histone H1/H5 (45). In the genomes of eukaryotic organisms, the DNA is wrapped around the four core histone proteins, which then join to form nucleosomes (46).

These nucleosomes further fold together into highly condensed chromatin to protect the genome from external influences. In doing so, it renders the genome extremely inaccessible to molecules or substances required for gene transcription, DNA replication, recombination, and repair (46). However, eukaryotic organisms break this repressive barrier through histone post-translational modifications, which typically involve covalently attaching certain chemical groups to histone residues at the N-terminal of amino acids. There are several histone post-translational modification mechanisms, but the most common ones are methylation, acetylation, phosphorylation, sumoylation, or ubiquitylation (40). Phosphorylation takes place on serine or threonine residues, methylation on lysine or arginine, acetylation and deacetylation on lysines, ubiquitylation on lysines, and sumoylation on lysines (47). Histone-posttranslational modifications restructure the chromatin into a condensed or non-condensed state, which determines the transcriptional and expression status of the associated DNA and genes. A non-condensed or open chromatin (euchromatin) is active, transcribes DNA, and expresses the embedded genes' functions. Condensed or closed chromatin (heterochromatin) is inactive, so it cannot transcribe DNA or express genes (48-49).

Of the four major histone post-translational modifications, methylation and acetylation are the most common, of which acetylation ideally

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de-condenses chromatin, while de-acetylation condenses chromatin (49). On the other hand, methylation either represses or expresses genes, depending on the gene region and degree of methylation, which can be either mono-, di-, or tri-methylated (50).

Histone post-translational modifications are caused by environmental factors such as nutrition, pollutant or chemical exposure, and pathogen exposure (40). Histone acetylation and methylation are catalyzed by histone acetyltransferases (HATs) and histone methyltransferases, respectively (HMTs). There are also enzymes called histone deacetylases (HDACs) and histone demethylases (HDMS), which do the work of deacetylation and demethylation, respectively (39).

Considering the effects of histone post-translational modifications on the expression of genes, abnormal histone modifications at the promoter or enhancer regions of genes that mediate immune function and beta cell development may predispose to T1DM. For instance, histone over-acetylation and over-methylation (e.g., H3K9Ac, H3K4me3, H3K9me2, 3, H3K27me3) near the promoter/enhancer regions of *HLA* genes (*HLA-DRB1* and *HLA-DQB1*) cause overexpression of the genes, resulting in an overactive immune system and thus predisposing to T1DM (51). Moreover, maintaining global silencing and terminal differentiation of beta cells in order to maintain beta cell identity requires a beta cell-specific chromatin regulatory system (44). So, epigenetic dysregulation involving chromatin restructuring in beta cells may predispose animals, including humans, to T1DM or T2DM. In addition, epigenetic dysregulation during B-cell activation following pathogen invasion may predispose to T1DM (52). In healthy individuals, the naive B cells in the immune system show an inactive epigenetic state characterized by genome-wide DNA over-methylation and histone deacetylation. However, upon encountering antigens, naive mature B cells divide and then differentiate into either plasma or memory B cells. This B-cell activation is preceded by genome-wide DNA hypomethylation, causing histone hyper-acetylation and over-expressed miRNAs. Normal histone modification is also essential for insulin gene expression and insulin secretion from islets in response to changing glucose levels, both of which are dysregulated in diabetes (53). The islet-specific *PDX1* gene also regulates insulin secretion via epigenetic mechanisms. In response to elevated glucose levels, *PDX1* recruits co-activators HATs p300 and CBP and a HMT SET7/9 (SET7), which increases the expression of H3/H4Kac and H3K4me2 at the insulin promoter, prompting the opening and thus transcription of chromatin, resulting in enhanced insulin secretion. In contrast, when there is not enough glucose, *PDX1* recruits co-repressors HDAC1 and HDAC2, which makes chromatin more compact and stops insulin production.

3. The role of non-coding RNAs in the etiology of type 1 diabetes

Non-coding RNAs (ncRNAs) are functional RNA molecules that act as cellular regulators. They are functional because they are transcribed from DNA but non-coding because they do not encode or are not translated into proteins (39). ncRNAs include transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs), small RNAs such as microRNAs (miRNA), small interfering RNA (siRNAs), and piwi interacting RNA (piRNAs), as well as long non-coding RNA (lncRNA) (39). ncRNAs influence gene expression at the transcriptional and post-transcriptional stages.

However, not all ncRNAs modulate epigenetic changes. Those that modulate epigenetic changes are classified into two, namely short ncRNAs (<30 nucleotides) and long ncRNAs (>200 nucleotides) (39). The short ncRNAs are subdivided into 3 groups, namely miRNAs, siRNAs, and piRNAs. miRNA and lncRNA disruptions are important pathways in the development of human diseases.

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Of all the ncRNAs, miRNAs and lncRNAs are the most studied and implicated in disease pathologies. miRNAs are small, single-stranded molecules of between 19 and 25 nucleotides (49). miRNAs interact with transcriptional and epigenetic regulators in cells to maintain lineage-specific gene expression (54). Specifically, miRNAs control the expression of genes during transcription by disrupting translation or degrading their target mRNA (55).

In most cases, miRNAs do this by interacting with the 3′ untranslated region (3′ UTR) of the target mRNA (56). But, in diseased cells, miRNAs' expressions are altered, leading to altered expression, mostly overexpression of the target genes (49). At a minimum, 6 out of every 10 protein-coding genes are expressed by miRNAs, whose disruption of their normal expression has been linked with many diseases, including T1DM (40). Regarding lncRNAs, they are localized in the nucleus or cytoplasm and play a role in numerous molecular processes that regulate gene expression, including epigenetic, transcriptional, and post-transcriptional regulation (57). lncRNAs do these by regulating mRNA-binding proteins and miRNAs, interacting with chromatin-remodeling complexes, or binding to transcription molecules or substances (57). Beta-cell growth and differentiation, apoptosis, insulin production, glucose metabolism, and insulin resistance are all regulated by lncRNAs (57). This suggests that aberrant lncRNA modifications may predispose to T1DM.

Studies have implicated miRNAs in autoimmunity, β-cell dysfunction, and apoptosis, which are hallmarks of T1DM. For instance, in individuals expressing autoimmunity, overexpression of miR-326 was observed in their peripheral blood lymphocytes (58-59). In addition, overexpression of miR-98, miR-23b, and miR-590-5p was also noticed in CD8+ T cells of individuals expressing T1DM (60). miRNA-510 was overexpressed, while miRNA-342 and miRNA-191 were repressed in Tregs of T1DM patients (61). In an analysis of human and mouse pancreatic islets and β-cell transcriptomes, over 1000 islet-specific lncRNAs that are constantly regulated by glucose were observed (62).

In non-obese diabetic mice, overexpression of four studied lncRNAs (pcDNA3_lncRNA-1, pcDNA3_lncRNA-2, pcDNA3_lncRNA-3, and pcDNA3_lncRNA-4) was observed, which correlated with the development of insulitis and progression to β-cell apoptosis (63). Because they do not break down, miRNAs and lncRNAs are good biomarkers for diagnosing and monitoring DM early (64).

Conclusion

Genetic and epigenetic modifications in genes regulate immune functions, such as *HLA*, *INS*, *CTLA-4*, and *PTPN22*, may cause autoimmunity of beta cells, leading to insulin insufficiency and T1DM. The mechanisms by which these genes and epigenetic modification cause T1DM are gene-specific, so treatment that targets the affected gene(s) in diabetic patients may result in better outcomes. Certain epigenetic changes are reversible, suggesting that reversing epigenetic changes in people with T1DM expressing epigenetic etiology may lead to a better outcome. Medical practitioners are urged to design T1DM treatments that particularly target the aforementioned genes and epigenetic changes in people who display such etiologies.

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Conflict of Interest

The authors declare no conflict of interest.

Authors' contributions

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T. Y: Conceptualized, wrote the original draft, and constructed an idea or hypothesis for research.

I. O, D. A and U. Sh: reviewed the article before submission not only for spelling and grammar but also for its intellectual content and wrote the body of the manuscript.

U. M and C. O: conducted the literature review.

All authors have accepted responsibility for the entire content of this manuscript and agreed to be accountable for all aspects of the study and resolved and approved the version to be published.

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