

# Epigenetic Mechanisms in Type-2 Diabetes Mellitus: A Narrative Review

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## ABSTRACT

The incidence of Type-2 Diabetes Mellitus (T2DM) has increased significantly in the last several decades, which is an important challenge for health professionals and researchers. The systems that mediate the interaction between environmental factors and the genes, such as epigenetics, may have a specific bearing on the aetiology of T2DM. With an emphasise on the part that epigenetics plays in the pathophysiology of T2DM, the present study attempts to give a thorough overview of the mechanisms behind disease initiation, possible biomarkers, and the consequences for T2DM. The findings suggest that  $\beta$ -cell malfunction, insulin resistance, and other metabolic abnormalities connected to T2DM are related to epigenetic alterations, which include histone modifications, Deoxyribonucleic Acid (DNA) methylation, and non coding Ribonucleic Acids (RNAs). Environmental factors that impact the development and course of the disease, including nutrition, exercise and pollution exposure, also have an impact on these epigenetic modifications. Knowing the complex interactions among genetics, epigenetics and environment is essential to pinpointing the precise aetiology of T2DM and creating customised treatment regimens. Epigenetic biomarkers could be helpful for risk assessment, early diagnosis, and tailored therapy for people with T2DM who are at risk or who have already been diagnosed. Future research must concentrate on unravelling the mechanistic understanding of the epigenetic pathways of T2DM in order to enhance therapeutic treatment and delve deeper into the pathophysiology of the condition.

**Keywords:**  $\beta$ -cell dysfunction, Environmental influences, Epigenomic biomarkers, Insulin resistance, Metabolic regulation

## INTRODUCTION

The T2DM is a chronic metabolic disorder characterised by high blood sugar levels resulting from the body's inability to properly use insulin. It is a prevalent condition worldwide, and its incidence has been steadily increasing over the past few decades [1]. Hyperglycaemia is a substantial risk factor for myocardial infarction, stroke, microvascular events and death in T2DM, which is a progressive illness [2]. The increasing prevalence of T2DM in recent decades cannot be solely attributed to genetic factors; environmental factors, including diet and lifestyle, are believed to contribute to this trend [3].

These factors have the ability to alter gene expression without modifying the DNA sequence, a phenomenon known as epigenetics. The term epigenetics describes modifications to DNA that result in variations in gene expression without altering the DNA sequence [4]. Epigenetic modifications involve chemical alterations that influence how the body interprets DNA. Extensive research has been directed towards investigating various epigenetic changes, such as DNA methylation, histone modifications and non coding RNAs. Researchers are looking into the function of epigenetics in the aetiology of T2DM in an attempt to find the missing piece of the disease's pathogenesis. Beyond DNA methylation, histone acetylation and gene silencing by non coding RNAs, other factors like addition/removal of phosphate groups (phosphorylation), ubiquitin-tagged degradation, disulfide bond formation and sumoylation are also considered as factors affecting epigenetics [5].

While genetic variables can have an impact throughout life and are fixed from birth, modifiable factors can operate as environmental exposures that either amplify or neutralise these genetic impacts [6]. When referring to the turning on or off of genes necessary to create the long-lasting alterations linked to the differentiation between several cell types [7].

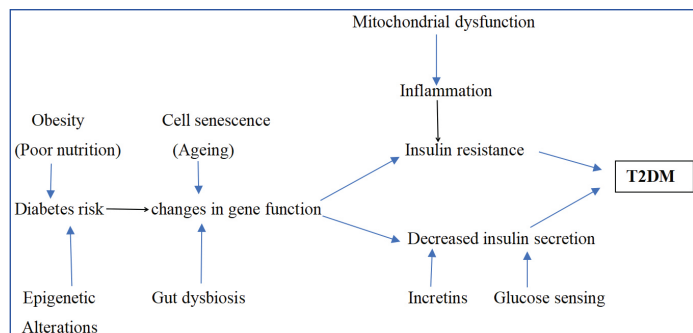
It is now evident that other processes are also at work in addition to DNA changes, like methylation of cytosine residues. Complex alterations may also affect the chromatin that surrounds the DNA [8]. The epigenetics changes, such as DNA methylation and histone

modifications, can impair the body's ability to regulate blood sugar levels, leading to the characteristic hyperglycaemia seen in T2DM [9]. In addition to DNA modifications, non coding RNA molecules, such as microRNAs and long non coding RNAs, also play a role in the epigenetic regulation of gene expression. These molecules can interact with messenger RNAs (mRNAs) and either enhance or suppress their translation into proteins [10]. Disruptions in the balance between these regulatory RNAs can have profound effects on cellular function and contribute to the development of metabolic disorders like T2DM [11].

Furthermore, environmental factors, such as diet and exercise, can influence the epigenetic landscape and contribute to the development of T2DM. For example, a previous study found that a high-fat diet can induce changes in DNA methylation patterns in adipose tissue, muscle and liver, which can affect the expression of genes involved in energy metabolism [12]. Similarly, regular physical activity has been associated with alterations in DNA methylation and histone modifications, leading to improved insulin sensitivity and glucose utilisation [13].

Studies on animals have shown that the expression of genes in chromatin that has been altered by histone Post-translational Modifications (PTM) contributes to the development of diabetes sequelae [14]. Overall, understanding the role of epigenetics in the development of T2DM is critical for the development of effective prevention and treatment strategies. By elucidating the molecular mechanisms underlying this complex metabolic disorder, researchers can identify potential therapeutic targets and biomarkers for early diagnosis. Various factors involved in causing the pathogenesis of T2DM are exhibited in [Table/Fig-1] [15].

The present study aimed to explore the role of epigenetics and its mechanisms in the aetiology of T2DM. A thorough search of the literature was performed to find epigenetic alterations linked to T2DM. To provide light on our present understanding of the molecular pathways implicated in the pathogenesis of T2DM, pertinent literature was evaluated, reviewed and reported.



[Table/Fig-1]: Overview of various factors leading to the pathogenesis of T2DM [15].

## Epigenetics in Human Disease

Through translational applications and the intricate interplay between genes and the environment, epigenetics provides crucial insights into the genesis and course of many diseases, like T2DM, cancer, cardiovascular disorders, neurological conditions (such as Alzheimer's disease) and autoimmune disorders (like rheumatoid arthritis), even beyond its molecular complexity [16]. Biochemical processes ranging from ageing and disease susceptibility to embryonic development and tissue differentiation are remarkably controlled by epigenetic pathways. Stable epigenetic inheritance and regulatory plasticity dynamically interact in a variety of contexts, including the genesis of illnesses, responses to physiological cues and cellular reprogramming events [17]. Environmental factors, such as stress, diet and chemical exposure, can have a substantial impact on the risk and course of disease. These factors can also produce major changes in epigenetic profiles [18].

Although genetics have a significant impact on the pathogenesis of T2DM, it is pivotal to understand the factors (chromatin level) that regulate blood glucose, starting with the site of insulin production and then to various epigenetic modifications. Hereby, the authors have discussed the role of beta cells of the pancreas in regulating T2DM, along with the vast genetic profiles and epigenetic alterations, like DNA methylation, histone modifications and non coding RNAs, involved in the development and succession of T2DM.

**The role of beta cells of the pancreas in T2DM:** Alpha and beta cells, two different types of pancreatic islet cells, can malfunction and cause dysregulated glucose homeostasis, as seen in T2DM. Insulin resistance and beta cell dysfunction are made worse by persistent low-grade inflammation, which is characterised by elevated levels of proinflammatory cytokines such Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) and Interleukin-1 $\beta$  (IL-1 $\beta$ ) [19]. Impaired autophagy, a cellular process that releases damaged proteins and organelles, aggravates the pathogenesis of T2DM [20]. Additionally, misfolded proteins cause oxidative damage and beta cell accumulation. The deregulation of microRNAs (miRNAs) in beta cells further exacerbates impaired insulin production and beta cell death in T2DM. Insulin sensitivity and beta cell function are significantly impacted by environmental factors, including diet, sedentary lifestyle and pollution exposure, in individuals with T2DM [21].

Research on mice that compared the importance of insulin and Insulin-like Growth Factor 1 (IGF-1) in high-fat diets found that the mice developed insulin resistance [22]. Furthermore, abnormalities in insulin signalling play a functional role in pancreatic beta cells by aiding in the aetiology of T2DM [23]. Hyperinsulinemia, a condition brought on by T2DM, is directly linked to an increased risk factor for Pancreatic Intraepithelial Neoplasia (PanIN), a type of cancer [24]. In streptozotocin-induced hyperglycaemia, research on mice shows that higher level of plasma IL-18 increase beta-cell size and proliferation, which in turn increases insulin output [25]. Molecular mechanisms have demonstrated that, in the context of diet-induced hyperinsulinemia and obesity, the expression of insulin receptors in KRAS G12D is required for hyperinsulinemia-driven PanIN formation [26]. This was also linked to increased translation of digestive

enzyme proteins, induction of local inflammation, and in-vivo PanIN metaplasia [27]. The combined effects of oxidative stress, Endoplasmic Reticulum (ER) stress, and decreased autophagy implicates a direct correlation between reduced beta cell mass and pathogenesis of T2DM [28]. A recent study compared T2DM patients and healthy controls for Body Mass Index (BMI) in the Japanese population showed that beta cell apoptosis further leads to reduced beta cell mass [29]. A study conducted on European population discusses that there is relatively lesser beta cell mass in T2DM compared with normal population [30].

## Alterations in genes involved in the pathogenesis of T2DM:

Several genes have been connected to the onset of T2DM [31]; variations in the expression levels or sequencing of these genes can affect the likelihood and progression of the disease [Table/Fig-2] [32].

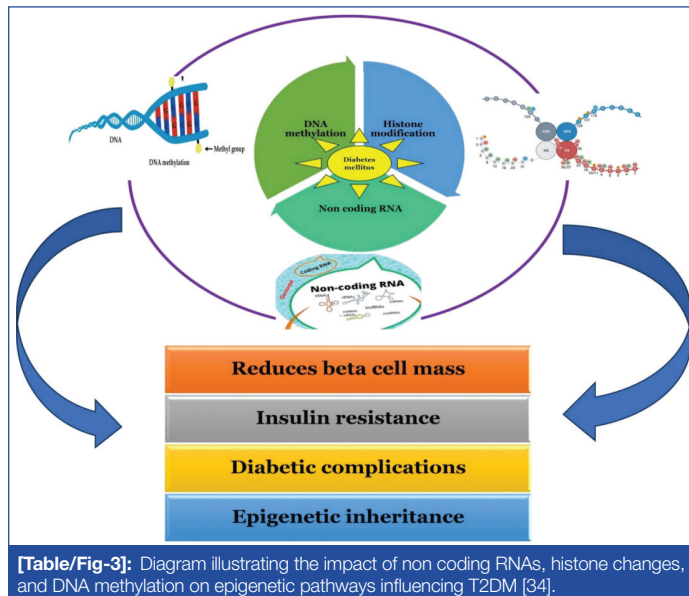
Gene	Polymorphism	Risk allele/genotype	Frequency
ABCC8	exon 22 C/T (codon 761)	T	0.01-0.03
ABCC8	intron 24 -3T/C	C	0.43-0.49
GCGR	Gly40Ser	Ser	0.01-0.02
GCK	3' CA repeat	z+4 allele	0.12
GCK	5 CA repeat	2 allele	0.04
INS	VNTR	Class III allele= large	0.33
INSR	SstI	5.8 kb allele	0.04-0.06
INSR	Val985Met	Met	0.01
IPF1	Asp76Asn	Asn	0.01
KCNJ11	Glu23Lys	Lys	0.37
PPARG	Pro12Ala	Pro	0.91
FRDA	GAA repeat	10-36 repeats	0.03-0.04
GYS1	XbaI	A2 site present	0.04

[Table/Fig-2]: Genes associated with pathogenesis of T2DM and their polymorphism [32].

**The INS gene:** This gene is one of the well-studied genes associated with T2DM because it generates insulin, the hormone necessary for glucose uptake and metabolism. Variations in the INS gene have been linked to decreased insulin production and susceptibility to T2DM. A key gene associated with insulin sensitivity and adipocyte growth, Peroxisome Proliferator-activated Receptor Gamma (PPARG), has also been connected to T2DM. The PPARG gene has been implicated in the development of insulin resistance and T2DM. Additionally, genes linked to insulin signalling pathways and pancreatic beta-cell function, such as Glucokinase (GCK), Hepatocyte Nuclear Factor 1 Alpha (HNF1A) and Insulin Receptor Substrate 1 (IRS1), have also been linked to genetic risk factors for T2DM. Variants in these genes may worsen the pathogenesis of T2DM by affecting insulin synthesis, insulin signalling, and glucose sensing [33]. Recent developments in genomic technologies, such as Genome-wide Association Studies (GWAS), have facilitated the identification of novel genetic loci associated with T2DM [32,33]. These studies have improved our knowledge of the underlying biological mechanisms of T2DM by identifying novel genes and genetic variants that raise the risk of the disease.

**Epigenetic mechanisms in T2DM:** T2DM is largely influenced by epigenetic pathways, which offer a comprehensive understanding of the disease that goes beyond hereditary predispositions [7]. In response to various internal and environmental stimuli, these mechanisms which include DNA methylation, histone modifications and non coding RNAs combine to control gene expression patterns, which eventually contributes to the pathophysiology of T2DM, as shown in [Table/Fig-3] [34]. The complex interactions among histone modifications, non coding RNAs and DNA methylation add to the multifactorial character of T2DM, underscoring the significance of epigenetics in clarifying the underlying molecular mechanisms of the illness [Table/Fig-3]. Understanding these epigenetic pathways has significant potential for the development of innovative therapeutic

approaches and individualised treatment plans with the goal of reducing the worldwide burden of T2DM has significant potential when these epigenetic pathways are well understood [35].



**DNA methylation in T2DM:** DNA methylation, one of the most extensively studied epigenetic modifications, involves the addition of methyl groups to cytosine residues within Cytosine phosphate Guanine (CpG) dinucleotides, primarily situated in gene promoter regions [36]. The alteration in DNA methylation patterns can result in the transcriptional silencing or activation of specific genes relevant to T2DM. For instance, hypermethylation of promoter regions of genes such as PDX1 and INS has been linked to impaired insulin secretion and  $\beta$ -cell dysfunction, key features of T2DM. DNA Methyltransferase 1 (DNMT1) is assumed to be the primary maintenance methyltransferase of the three DNMTs, with enzymatic activity probably by Ubiquitin-like with {Plant Homeodomain (PHD)} and Ring Finger domains 1 (UHRF-1), help because they recognise the hemi-methylated sites [37]. DNMT3a and DNMT3b are involved in the maintenance of DNA methylation patterns, which would mostly methylate the sites that are probably missed by DNMT1. Numerous investigations that examined the connection between alterations in DNA methylation and gene expression in islets from donors with T2DM using a candidate gene method [38].

In a study, 1,649 CpG sites and 853 genes, including Tcf7l2, Fto, Kcnq1, Irs1, Cdkn1a and Pde7b, were shown to have significantly different DNA methylation in human islets from T2DM donors compared to controls, using the genome-wide Infinium 450K array [39]. The study conducted by Davegårdh C et al., examined the alteration patterns involved in the methylation of human pancreatic DNA among T2DM and non T2DM, well explained the epigenetic mechanisms that contribute to the prevalence of diabetes [40].

A previous study has found DNA methylation of genes such as INS, PDX1, PPARGC1A, and GLP1R in human pancreatic islets of donors with T2D and non diabetic controls. These genes may be linked to the development of T2DM [41]. Islets from the T2DM have increased DNA methylation compared to those from normal individuals [42]. Studies found altered DNA methylation in adipose tissue, liver and pancreas islets. Due to T2DM being polygenic, specific CpG sites are unlikely to show methylation [43].

**A role for histone modifications:** The role of histone modifications, like DNA methylation, acetylation and small non coding RNAs like miRNAs, embarks the phenotypical changes without altering the DNA sequence [44]. PTMs of histones symbolise the epigenome. Genome-wide profiling of histone PTMs has shown that different patterns of particular histone modifications can differentiate critical

repeated elements, gene bodies, enhancers and promoters, which are examples of regulatory areas [45].

**Role of non coding RNAs and T2DM:** Further highlighting the role of epigenetic mechanisms in the disease process, dysregulation of miRNAs and Long non coding RNAs (lncRNAs) has been identified in T2DM Mellitus (T2DM), affecting insulin production,  $\beta$ -cell function, and peripheral insulin sensitivity. lncRNAs are types that have limited protein-coding potential and function as regulatory molecules in epigenetics and at post-transcriptional levels [46]. lncRNAs such as LY86-AS1 and HCG27\_201 have been found to be downregulated in individuals with T2DM. Specifically, LY86-AS1 could potentially be used as a biomarker for the pathogenesis of T2DM [47].

**Histone deacetylases and T2DM:** Histone acetylation and deacetylation are key epigenetic mechanisms. Acetylation favours gene transcription and weakens the interaction between histones and DNA, while deacetylation by Histone Deacetylases (HDACs) inhibits gene transcription. This process is considered a PTM of proteins [48]. One such example of HDACs is the administration of sodium butyrate that ameliorates hyperglycaemia and serum cholesterol levels in T2DM rats induced by high fat and streptozotocin by downregulating the Protein kinase R-like Endoplasmic Reticulum Kinase-C/EBP Homologous Protein (PERK-CHOP) pathway, which is associated with ER stress expressing proteins [49]. Some of the HDAC inhibitors used in inhibition of gene transcription is shown in [Table/Fig-4].

HDAC inhibitor	Animal model	Outcome
1. Sodium butyrate 2. Trichostatin A	Male-C57BL/6J mice	Increased insulin sensitivity and energy expenditure
3. Sodium butyrate	Male calves	Improved insulin sensitivity
4. Tributyrin	C57BL/6 male mice	Attenuated high lipid levels
5. Valproic acid	Streptozotocin induced Sprague Dawley rats	Increased beta cell proliferation

**[Table/Fig-4]:** HDAC inhibitors used in histone deacetylation.

### The Emerging Role of Epigenetics in the Pathophysiology of Gestational Diabetes Mellitus (GDM):

A major health risk during pregnancy is Gestational Diabetes Mellitus (GDM), which has impact on the health of both the mother and the foetus. Recent studies have revealed the complex role that epigenetic pathways play in the pathophysiology of GDM, opening up new possibilities for studying and even treating this illness [50,51]. A landmark study titled 'The Emerging Role of Epigenetics in the Pathophysiology of GDM' explained that DNA methylation, which is pivotal for the maintenance of gene expression in promoter regions, is not restricted only to CpG regions but also includes non CpG regions. Therefore, any epigenetic changes will also influence offspring and its future life [51]. Hence, a complete analysis of epigenetic alterations, due to their reversible nature, must be studied thoroughly to prevent discomfort or poor quality of life in the future. Recent interest has been in downregulating Histone Deacetylase 2 (HDAC2) in GDM patients [52,53]. By eliminating acetyl groups from histone proteins, HDAC2, a member of the histone deacetylase family, is essential in regulating chromatin shape and gene transcription. The expression of genes involved in important metabolic processes is impacted by abnormal histone acetylation patterns caused by deregulation of HDAC2 activity [53].

Further, HDAC2 downregulation affects cellular processes associated with GDM in addition to chromatin remodelling. Interestingly, decreased HDAC2 levels in GDM patients have been linked to impaired mitochondrial activity and increased inflammatory responses [54].

## CONCLUSION(S)

Epigenetics research on T2DM has shown a complicated network of molecular complexity, gene-environment interactions and developmental antecedents. This comprehensive study



examined the effects of epigenetic alterations on T2DM from many perspectives, based on fundamental reviews and studies.

In conclusion, the present review offers several insights on T2DM epigenetics. Different perspectives, statistical data and analytical methods help understanding of gene-environment interactions and T2DM development. This knowledge shapes diabetes research and guides the development of targeted therapies, individualised medicine, and well-informed healthcare policy. As we study, epigenetic complexities, we imagine a future where T2DM is understood not only by molecular precision but also by the dynamic interaction between genes, environment and early-life exposures.

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