GENETIC AND EPIGENETIC CONTRIBUTIONS TO THE PATHOGENESIS OF TYPE1 & TYPE2 DIABETES

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

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Approval

The thesis is titled "Genetic and Epigenetic Contributions to the pathogenesis of Type1 & Type2 Diabetes" submitted by Mehnaz Islam Tanha (22146087), of Spring 2022, has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) in January, 2026.

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Ethics Statement

This project does not involve any kind of animal and human trial.

Abstract/ Executive Summary

This thesis explores the genetic and epigenetic contributions to the pathogenesis of Type 1 and Type 2 diabetes mellitus, two of the most prevalent global metabolic disorders. It highlights the etiological distinctions between autoimmune beta-cell destruction in Type 1 diabetes and insulin resistance with beta-cell dysfunction in Type 2 diabetes. The work synthesizes evidence on HLA class I and II loci, insulin gene polymorphisms, and non-MHC variants that predispose individuals to Type 1 diabetes. It further examines epigenetic mechanisms, DNA methylation, histone modification, and non-coding RNAs that modulate gene expression and immune tolerance. Clinical manifestations, risk factors, and systemic complications are contextualized within the global epidemiological burden of diabetes. The thesis underscores the interplay of genetic susceptibility and environmental triggers, shaping disease onset, progression, and heterogeneity. Tables and figures provide structured clarity on symptoms, genetic loci, and pathogenic cascades, enhancing comprehension for clinical and research audiences.

By integrating molecular insights with epidemiological data, the study emphasizes the need for precision medicine in diabetes management. It contributes to academic discourse by bridging basic science and translational relevance, offering a framework for future therapeutic strategies.

Overall, the thesis demonstrates scholarly rigor, strong synthesis of literature, and clear articulation of diabetes as a multifactorial disorder requiring multidisciplinary intervention

Keywords: Diabetes Mellitus, Type 1 Diabetes, Type 2 Diabetes, Genetic Susceptibility, Epigenetic Mechanisms, HLA Genes, Insulin Resistance, Autoimmunity, Precision Medicine, Pathogenesis

Dedication

I lovingly dedicate this thesis to my father, whose memory remains a guiding light in my life.

Acknowledgement

Firstly, I would like to express my sincere gratitude to Mushtahsin Ferdousi miss, whose exceptional mentorship has been invaluable. Furthermore, I am sincerely thankful to Dr. Sharmind Neelotpol, the chairperson and Dr. A.F.M. Yusuf Haider the acting dean of the school of pharmacy, for their support and dedication in ensuring a nurturing academic atmosphere. Their contributions have been instrumental in shaping my learning experience.

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List of Acronyms

- ADA – American Diabetes Association
- CDC – Centers for Disease Control and Prevention
- DNA – Deoxyribonucleic Acid
- HLA – Human Leukocyte Antigen
- INS – Insulin Gene
- IR – Insulin Resistance
- MHC – Major Histocompatibility Complex
- NK – Natural Killer (cells)
- PTPN22 – Protein Tyrosine Phosphatase, Non-Receptor Type 22
- T1D – Type 1 Diabetes
- T2D / T2DM – Type 2 Diabetes Mellitus
- T1DGC – Type 1 Diabetes Genetics Consortium
- Treg – Regulatory T-cell
- VNTR – Variable Number Tandem Repeat
- IL2RA – Interleukin-2 Receptor Alpha
- CTLA4 – Cytotoxic T-Lymphocyte Antigen 4
- TCF7L2 – Transcription Factor 7-Like 2
- IGF2BP2 – Insulin-Like Growth Factor 2 mRNA-Binding Protein 2
- PPARG – Peroxisome Proliferator-Activated Receptor Gamma
- KCNJ11 – Potassium Inwardly Rectifying Channel Subfamily J Member 11
- FTO – Fat Mass and Obesity-Associated Gene
- IRS1 – Insulin Receptor Substrate 1
- SLC30A8 – Zinc Transporter

Chapter 1

Introduction

1.1 Background:

Diabetes has become one of the most common and globally known diseases, affecting hundreds of millions of people across diverse age groups and regions (Hill-Briggs et al., 2021). It is basically a defect of metabolism due to elevated levels of blood glucose in the body, leading to obstruction in the production, section, and overall activities of the hormone named insulin (American Diabetes Association, 2024; Park et al., 2021). Insulin is one of the most significant hormones that is prepared and secreted by pancreatic beta-cells in our body and acts as the key of regulating the blood glucose levels (Kolb & Martin, 2017; Park et al., 2021).

In simple terms, insulin helps glucose to get into our body's cells from the bloodstream, where it is used for energy. So without adequate amounts of insulin or if our body doesn't react to it properly, the blood glucose level can rise, resulting in conditions like diabetes mellitus (Rosen et al., 2018; Siddiqui et al., 2024).

All of these may sound simple, but if the blood sugar levels remain high and untreated for a prolonged period, it can lead to a wide range of complexities-some acute, some are chronic, but mostly long-term complications. Poorly managed diabetes can lead to cardiovascular, neurological, ophthalmic complications, kidney damages, and many more (Damiano et al., 2024; Reddy et al., 2015).

The pathophysiological cascade of diabetes mellitus, from genetic triggers to systemic complications, is illustrated below in Figure 1.

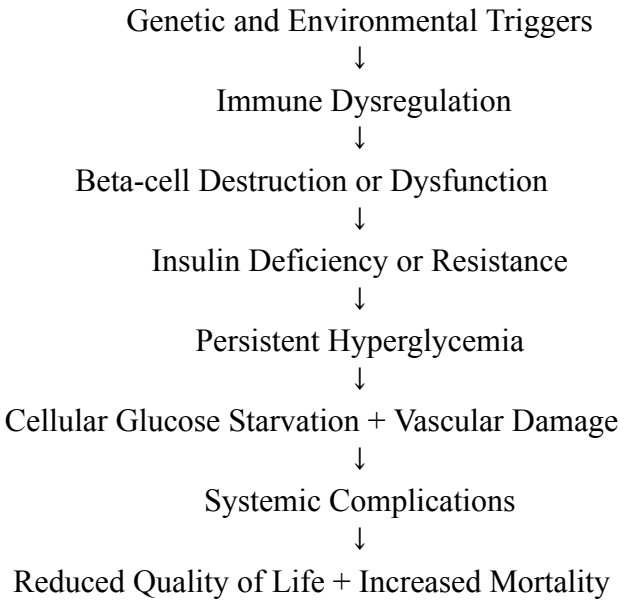

Figure 1: Pathophysiological cascade of diabetes mellitus, from genetic triggers to systemic complications (Damiano et al., 2024; Kolb & Martin, 2017; Rosen et al., 2018).

Overall, diabetes mellitus impacts the quality of life in individuals, and as a fastest-growing disease, it has created an alarming situation, placing tremendous pressure on healthcare systems worldwide (Chen et al., 2025; Richards et al., 2022). In case of global prevalence, an estimated 589 million people around the age of 20-79 are living with diabetes across the world. Moreover, about 1 in 9 adults, as of 2025 (International Diabetes Federation, 2025). By 2050, it is predicted to reach 853 million, which means 1 in 8 adults will be affected (Institution for Health Metrics and Evaluation, 2023). Over 40% people with diabetes are still undiagnosed globally, especially in middle and low developed countries (International Diabetes Federation, 2025).

It has become one of the major obstacles in the public health sector of the 21st century, with its fast and constant increase due to a combination of urbanization & lifestyle changes, biological,

socioeconomic, environmental factors, and so on (Hu, 2011; Kolb and Martin, 2017). Beyond the clinical manifestations, diabetes mellitus is not just a disorder shaped by these external factors but it's way more complex (DeFronzo et al., 2015). There are underlying genetic predispositions and epigenetic modifications as well which play a big role in why some people develop this and others don't (Ahmed et al., 2020; Rosen et al., 2018). These factors also influence how our bodies will respond to the secretion and action process of insulin, disease susceptibility, progression and individual variations (Ashcroft & Rorsman, 2012).

1.2 Classification

Primarily based on the etiological differences, which refers to the distinct causes or origins of each condition, and different pathophysiological mechanisms, which relate to the physical and biochemical changes occurring in the body during each condition, diabetes mellitus is categorized into two classes- Type 1 Diabetes & Type 2 Diabetes (Dhawan & Natarajan, 2019; Jazieh et al., 2024).

Type 1 Diabetes:

This is initially a self-reactive disorder. In this condition our body's natural defense system unintentionally strikes and kills the beta cells present in the pancreas that produce insulin hormone (Thompson et al., 2023). As Atkinson et al. (2014) describe, this autoimmune response is generally driven by a process called insulitis, in which T-lymphocyte cells infiltrate the islets (entry and accumulation of T-lymphocytes into the islets of Langerhans) causing complete devastation of the beta cells, which leads to a major shortage of insulin in the body, resulting in the blood glucose level to rise. This condition is referred to as Type 1 diabetes (La Noce et al., 2022). According to Craig et al. (2020), it is approximately 5-10% of all diagnosed diabetes

cases across the world till now. The population is near 9.2 million and it is expected to double by 2040 (Patterson et al., 2019). It is mostly seen in children, adolescents and young adults, with the highest incidence occurring between ages 10-14 (Craig et al., 2020). However, it can be developed at any age (Harding et al., 2022).

Type 2 Diabetes:

This is the most frequent and widespread metabolic disorder(over 90% of diabetes cases) that develops gradually in the human body (DeFronzo et al., 2015). It results from a combination of two main problems: the pancreatic beta cells fail to release insulin hormone adequately, and insulin resistance, in which condition our body tissues fail to respond enough to insulin (Ashcroft & Rorsman, 2012). Since insulin is so important for balancing blood sugar extents, including the whole process, it is so strictly regulated; any defects in the mechanism cause metabolic imbalance and may lead to diabetes (Kahn et al., 2006). Usually, in T2DM development, the beta cell dysfunction is more dangerous than IR (Esser et al., 2020). However, if both of these issues appear together in the pathogenesis, they worsen hyperglycemia and drive the growth of type 2 diabetes (Weir & Bonner-Weir, 2004).

The classification of diabetes is not only based on clinical and pathological features but also considers underlying hereditary and epigenetic influences that contribute to the onset and advancement of the disease (Dayeh & Ling, 2015).

1.3 Symptoms:

Common symptoms of type 1 and type 2 diabetes are given in table 1 (SpringerOpen, 2024; Mayo Clinic, 2024; Brady et al., 2022; Drivsholm et al., 2005):

Table 1: Common symptoms of Type 1 and Type 2 Diabetes

Type 1 Diabetes	**Type 2 Diabetes**
Immoderate urination (polyuria)	Slow healing of cuts & wounds
Constant thirst (polydipsia)	Increased thirst
Fatigue or weakness	Fatigue or weakness
Reduced weight	Weight loss
Blurry vision	Fluctuating vision
Rapid breathing(kussmaul respiration)	Frequent urination
Increased hunger	Confusion, Sleep disturbance
Irritable or moody feeling	Numbness, tingling sensation in hands or feet
Nausea, vomiting, stomach discomfort	Gastrointestinal discomfort, Edema

1.4 Risk Factors:

Diabetes is a condition that develops and grows in the body due to the negative contribution of several factors or influences (Zheng et al., 2018). This malfunctioning condition is majorly shaped by inherited tendencies, lifestyle, physiological, and environmental changes over time as they compromise insulin secretion, function, and glucose control (Kolb & Martin, 2017; Greenbaum et al., 2025). These contributing elements vary across populations, regions, and life stages, making diabetes a complex disease that requires heavy observation, personalized

understanding, and professional management strategies (Galindo et al., 2023; Cheng et al., 2025). Both the disease contributing factors and management systems are different in the case of both types of diabetes (Craig et al., 2020). The figure below shows the systemic effects of diabetes on various organs of our body.

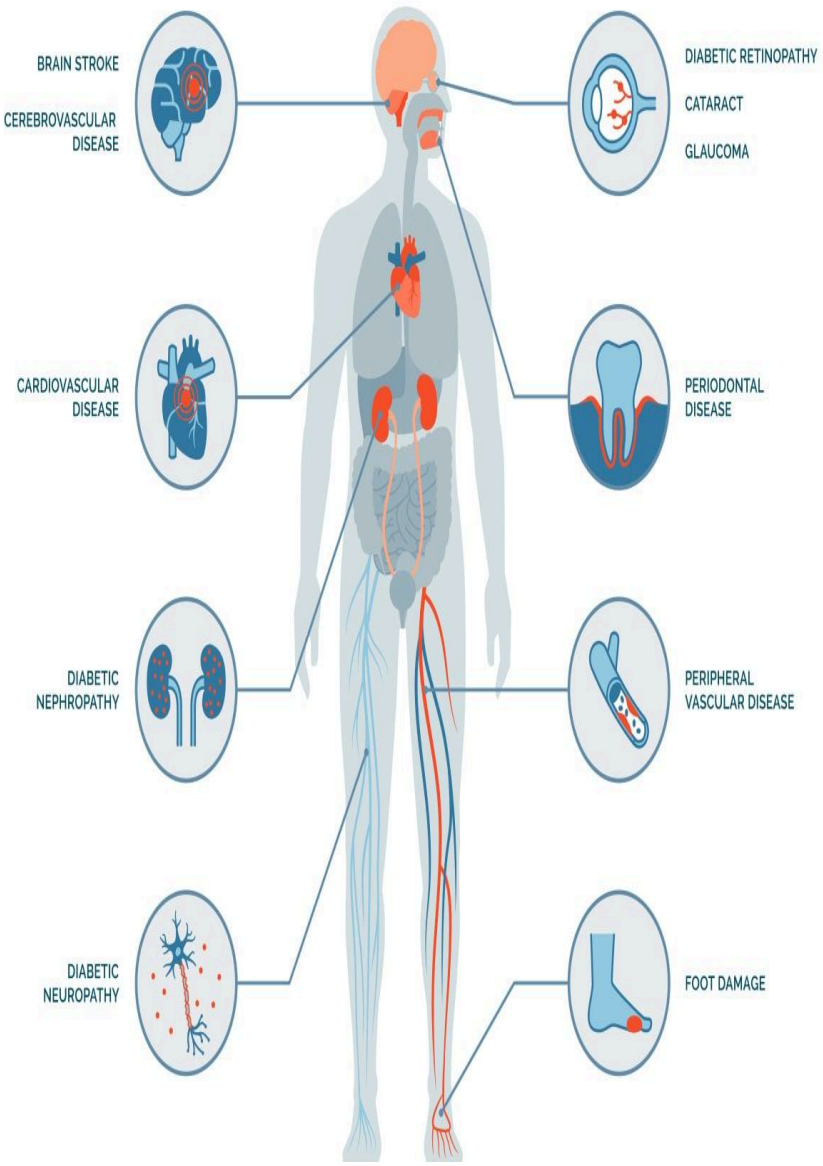

Figure 2: Systemic effects of diabetes on various organs of the body (Endocrine Society, 2022)

Genetic Elements in the development of type 1 diabetes

As a self-reactive condition, type 1 diabetes is highly influenced by genetic disposition, besides the environmental factors (Knip et al., 2005). In this case, our body's defense system unintentionally or mistakenly strikes and destroys the insulin-producing beta-cells (Knip et al., 2005). The onset of this condition is highly influenced by family history and genetics (Esposito et al., 2019). As per studies, the chances of developing type 1 diabetes increase 3-6% in an individual if his/her parents have the same condition, and the risk jumps to 8-10% if a sibling has it (Parkkola et al., 2013; Turtinen et al., 2019). Although this percentage varies due to several other factors, such as population and region (Cheng et al., 2025). The body's defense system is significantly influenced by various genetic factors in its ability to discriminate between self and non-self, leading to autoreactive T-cell responses against pancreatic beta-cells (Noble et al., 2010). Moreover, this susceptibility is polygenic, which means multiple genes are involved in the onset of the condition (Nejentsev et al., 2007). However, not all of the factors directly act in developing the disease but interact with environmental triggers, causing individual risk profiles (Knip et al., 2005).

Based on twin and family studies, researchers have found that, within the European population, approximately 50% likelihood of developing type 1 diabetes is dependent on hereditary factors (Luckett et al., 2023; Tait, 2024).The Major Histocompatibility Complex (MHC) area and the human leukocyte antigen (HLA) locus are the major sectors where the primary factor contributing to this genetic risk and its variations are located (Michalek et al., 2024; Nejentsev et al., 2007). MHC is a section of DNA located on the short arm of chromosome 6 in the human genome, which is densely packed with over 200 genes that are crucial for our immune system to function (Matzaraki et al., 2017; Allcock, 2012). HLA is a group of genes present in the MHC (on chromosome 6p21) region that code the protein that helps our defense

system to discriminate between self and non-self (Garrido, 2024; Noble & Wan, 2024). HLA genes are divided into 3 classes (Shiina et al., 2009). Class I incorporates HLA-A, HLA-B, HLA-C genes; class II includes HLA-DR, HLA-DQ, HLA-DP & lastly, class III incorporates TNF, complement proteins, and heat shock proteins (Turicek & Wan, 2025; Tait, 2024). Among all these genes, class I & II HLA genes are directly involved in the onset of T1D (Noble & Wan, 2024). Class III genes are also involved but in an indirect way (Trowsdale & Knight, 2013). Some studies show that they may modulate autoimmune activity, but they don't carry the same predictive weight, and their role is not as critical as class I & II (Noble & Wan, 2024). Apart from the HLA genes, there are many additional genetic factors (more than 90) discovered by the Type 1 Diabetes Genetics Consortium (T1DGC) & other other international efforts (Onengut-Gumuscu et al., 2025). Most of these newly discovered genes are located in noncoding regions and undergo polymorphism (Onengut-Gumuscu et al., 2025). All of these individually have small impacts as they don't make protein directly, but influence others and together increase the overall risk (Onengut-Gumuscu et al., 2025; Tait, 2024).

Some of the major MHC and non-MHC genes that come up with the pathogenesis of Type-1 diabetes are mentioned below (Tait, 2024; McGrail et al., 2025):

- **Class I HLA Genes:** A class of HLA molecules that is present in all nucleated cells in mammals, which present intracellular antigens (internal proteins or peptides) to CD8+ cytotoxic T cells and can directly attack pancreatic beta cells (Noble et al., 2010; Tait, 2024). Three major genes are involved here:
    1. **HLA-A:** These class I MHC genes present insulin-producing beta-cell peptides to immune cells called CD8+ T cells (Bettini & Vignali, 2011). These genes actually display small bits of what is happening inside the cells to the CD8+ T cells (Bettini & Vignali, 2011). These T cells appear to be dangerous or abnormal as

they may attack and destroy insulin-producing beta cells by mistakenly considering the peptide fragments present inside the beta cells as harmful substances (Bettini & Vignali, 2011). Variants such as A24:02 and A02:01 facilitate the immune system to attack these cells, increasing the risk of type 1 diabetes (Koeleman et al., 2024).

2. **HLA-B:** It's the strongest connected gene with T1D among all the genes included in class I HLA(Nejentsev et al., 2007). Like HLA-A genes, HLA-B genes can also present insulin producing beta-cell peptides to CD8+ T-cells but they are more strongly linked to triggering autoimmune attacks on beta cells because of their risk allele B39:06, which causes the immune system to attack more aggressively (Koeleman et al., 2004). This, in turn, increases the chances of the development of type 1 diabetes (Noble et al., 2010; Tait, 2004).
3. **HLA-C:** Compared to HLA-A and HLA-B genes, HLA-C genes play a relatively small role in the pathogenesis of type 1 diabetes by acting indirectly (Roark et al., 2014). These help CD8+ T cells to recognize peptides (Bettini & Vignali, 2011). Furthermore, the HLA-C gene works with natural killer (NK) cells, which function as a first line of defense in the body's immune system (Roark et al., 2014). Additionally, HLA-C alleles (HLA-C07:01 and HLA-C07:02) show a moderate connection with T1D through their influence on HLA-B alleles (Roark et al., 2014). They also support T1D susceptibility by shaping the immune responses through affecting the inflammatory environment in pancreatic islets (Roark et al., 2014; Tait, 2024).

- **Class II HLA Genes:** These genes are very crucial for initiating immune responses in our body (Nejentsev et al., 2007). Primarily, they involve recognizing exogenous

proteins, such as viruses or food particles, or presenting antigens to CD4+ helper T cells (Nejentsev et al., 2007). However, in certain cases, class II HLA genes can mistakenly confuse the immune system by detecting normal beta cell proteins like insulin as if they are harmful (Noble et al., 2002). This confusion triggers the immune system to attack on those insulin producing cells,which finally leads to the strongest genetic association with type 1 diabetes (Nejentsev et al., 2007). Three major genes which are generally expressed on antigen-presenting cells are included in class II Human Leukocyte Antigen (HLA) genes (Erlich et al., 2008). These genes are: (Erlich et al., 2008)

1. **HLA-DR:** These are basically MHC class II cell surface receptors located on chromosome 6 (Nejentsev et al., 2007). These proteins help the immune system by presenting external antigens to CD4+ helper T cells by forming the peptide binding groove (Noble et al., 2002). However, certain HLA-DR alleles, such as HLA-DRB1*03 (DR3) or HLA-DRB1*04 (DR4) can mistakenly present normal beta proteins like insulin, as threats and this autoimmune destruction can create a strong link to type 1 diabetes (Erlich et al., 2008).
2. **HLA-DQ:** Class II HLA genes, which play a very crucial role in the defense system by differentiating among self and non self (Noble et al., 2002). These include two subunits: DQA1 and DQB, which are composed of alpha and beta chains (Nejentsev et al., 2007). The chief function of HLA-DQ is to present extracellular peptide antigens like pathogens or self proteins to CD4+ T helper cells (Nejentsev et al., 2007). However, certain HLA-DQ alleles work with HLA-DR alleles, forming combinations e.g, HLA-DRB1*03 (referred to as DR3) and HLA-DRB1*04 (addressed as DR4) with DQB1*03:02 (known as DQ8), which are strongly connected with the progression of type 1 diabetes as these

variants can misidentify normal beta cell proteins as dangers, triggering a self reactive response that leads to progressive obliteration of insulin producing beta cells (Noble et al., 2002).

3. **HLA-DP:** Like HLA-DQ, HLA-DP is also composed of two subunits (DPA1 & DPB1) containing alpha and beta chains and together they influence the immune system similarly like HLA-DP (Erlich et al., 2008). In case of type 1 diabetes progression, HLA-DP plays comparatively a less dominant role than the other two HLA genes (Awata et al., 2001). Yet certain alleles like DPB1*0301 and DPB1*0202 may still affect the functions of the defense system to the beta cells and can elevate the chances of T1D (Awata et al., 2001).

Insulin Gene: A non-MHC gene that produces the human insulin hormone (Pugliese et al., 1997). It encodes preproinsulin, which is the precursor to insulin (Pugliese et al., 1997). This gene generally expresses insulin hormone at a low level to help the immune system develop tolerance to beta cell antigens (Vafiadis et al., 1997). However, this thymic expression can be affected due to certain polymorphism in the INS gene, especially in the VNTR (variable number tandem repeat) region (Kukko et al., 2005). Among all the polymorphic variants, the class 1 VNTR alleles cause impaired immune tolerance by reducing thymic insulin expression. This action results in an increased autoimmune attack on pancreatic beta cells, leading to type 1 diabetes (Kukko et al., 2005).

- **PTPN22:** Also called “Protein Tyrosine Phosphate, Non-Receptor Type 22”. It is a gene that encodes a protein named “Lymphoid Tyrosine Phosphatase” (LYP) (Begovich et al., 2004). Its main function is to keep in check the immune responses of our body by negatively regulating T-cell receptor signaling (Begovich et al., 2004). However, a

polymorphic variant or allele of this gene, C1858T, also known as R620W, affects this action as it can alter the LYP protein's ability to interact properly with CSK (a tyrosine-protein kinase that keeps T-cell activity in check) (Viken et al., 2010). This dysfunction leads to hyperactivation of T-cells, which increases the risk of autoimmune destruction of insulin-producing beta-cells in the pancreas, resulting in the progression of type 1 diabetes (Simeonov et al., 2010).

- **CTLA4:** One of the critical proteins that acts as a key immune checkpoint on T-cells is cytotoxic T-Lymphocyte Antigen 4 (Ueda et al., 2003). It helps slow down immune responses (Ueda et al., 2003). Certain polymorphic variants of the CTLA4 gene, such as G49A and C60T, are linked with the development of T1D as they reduce the ability to regulate T-cells properly and cause hyperactivated immune responses, resulting in mistaken attacks on insulin-producing beta cells (Kavvoura & Ioannidis, 2011; Anjos et al., 2002).
- **IL2RA:** Interleukin-2 Receptor Alpha(IL2RA), also known as "CD25" is a protein which is located in the IL-2 receptor complex and very important for the growth and activities of regulatory T-cells or Tregs (the cells that prevent autoimmunity) (Lowe et al., 2007). Single nucleotide polymorphism in this gene has been proved to be associated with T1D susceptibility as it can reduce the IL-2 signaling which weakens Treg function, promoting harmful autoimmune responses (Dendrou et al., 2009). As a result, T-cells may attack on the beta cells present in the pancreas, aiding in the development of type 1 diabetes (Dendrou et al., 2009; Maier et al., 2008). The summarized genetic triggers and their outcomes in Type 1 diabetes are presented in Table 2 (Tait, 2024; Noble & Wan, 2024; Onengut-Gumuscu et al., 2025).

Table 2: Genetic triggers and their outcomes in Type 1 Diabetes

TRIGGER	GENETIC IMPACT	OUTCOME
Class I HLA Genes	Present intracellular beta-cell peptides to CD8+ T-cells; certain alleles enhance autoreactive cytotoxic responses.	Direct beta-cell destruction via cytotoxic T-cell activation.
Class II HLA genes	Present extracellular antigens to CD4+ T-cells; some alleles misidentify beta-cell proteins as threats.	Strongest genetic association with T1D; initiates autoimmune cascade.
Insulin Gene	Polymorphism in the VNTR region reduces thymic insulin expression, impairing central immune tolerance.	Increased risk of autoreactive T-cell escape and beta-cell targeting.
PTPN22	R620W variant disrupts T-cell receptor signalling regulation, leading to hyperactive T-cell responses.	Heightened autoimmune attack on pancreatic beta-cells.
IL2RA	SNPs reduce IL-2 signaling, weakening regulatory T-cell (Treg) function.	Impaired immune tolerance, enhanced autoreactive T-cell activity.

There are many more non-MHC gene or locus such asTYK2 (Tyrosine Kinase 2), IL10 (Interleukin 10), GATA3 (GATA Binding Protein 3), CD226 (Cluster of Differentiation 226), SH2B3 (SH2B3 Adaptor Protein 3) and many more (more than 90) that contribute in the

advancement of type 1 diabetes (Marroqui, 2015; Liu, 2009; Ozgur, 2003; Brown, 2024; Watson, 2025).

Epigenetic Contributions to Type 1 diabetes pathogenesis:

The chemical adjustments that affect gene activity while not modifying the actual underlying DNA sequence are identified as epigenetic factors (Stankov et al., 2013). They act like switches that can turn on or off the genes or simply adjust the expressions of genes (Jerram et al., 2017). These chemical modifications can be done by epigenetic mechanisms such as DNA methylation (adding methyl groups to DNA, silencing gene expression), histone modification (altering the structure of chromatin) and non-coding RNAs (regulating gene expression post-transcriptionally) (Cerna, 2020). Unlike genetic factors, epigenetic factors are reversible and are affected by environmental influences such as lifestyle, hormonal changes, environmental exposures (pollution or toxins), stress, infection, aging, pregnancy, and many more (Mio et al., 2022). Epigenetic factors are the reason why two people with similar genetic makeup go through different disease conditions(Zhang et al., 2021; Stankov et al., 2013).Epigenetic variables have been demonstrated to function as a conduit connecting risk genes and environmental stressors, hence augmenting the susceptibility and complexity of type 1 diabetes (Cerna, 2020). They can modify the actions of immune cells and insulin-producing pancreatic beta-cells, which further leads to autoimmune destruction and finally diabetes (Jerram et al., 2017).

Major Epigenetic Programs Involved in Type 1 Diabetes Development

The group of molecular activities that chemically modify gene function without altering the underlying gene sequences are known as epigenetic mechanisms (Feinberg, 2007; Bird, 2007). The core epigenetic mechanisms that are accountable for the onset and advance of type 1 diabetes are mentioned below (Rakyan et al., 2011; Knip et al., 2012):

DNA Methylation:

It simply points out the methyl groups (-CH3) addition to DNA, mainly at the CpG islands of the cytosine bases in DNA, which are basically the gene promoter regions (Jones & Baylin, 2007; Moore et al., 2013). This chemical modification suppresses gene transcription or silences gene expression by blocking transcription factor binding (Feinberg, 2007; Bird, 2007). However, research shows that the key regulatory genes (e.g., HLA, INS, FOXP3) in the human body undergo this methylation process and disrupts immune tolerance, promoting autoimmunity (Rakyan et al. 2011; Morahan et al., 2009; Lal et al., 2009). All of these modifications are triggered or activated by environmental influences (Feinberg, 2007; Knip et al., 2012).

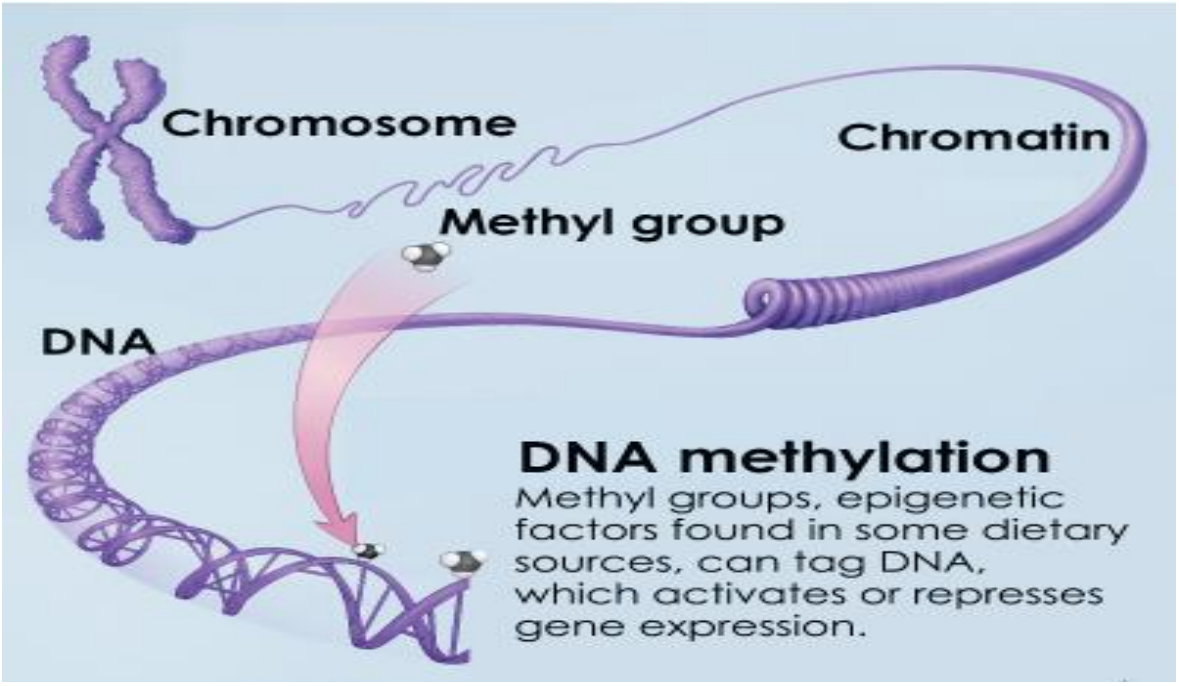

Figure 3: DNA methylation process in epigenetic regulation (National Eye Institute, 2023).

Histone Modification: Histones are a very crucial protein in our body (Bannister & Kouzarides, 2011). They package and organize DNA into chromatin, playing a crucial

role in gene regulation, expression, protection, and chemical modification that are important for cellular processes such as acetylation, methylation, phosphorylation (Zhang & Dent, 2005; Kouzarides, 2007). These chemical modifications do not change the underlying DNA sequence; instead, they determine how tightly DNA is packed, controlling the transcriptional machinery of specific genes (Jenuwein & Allis, 2011; Feinberg, 2007). Moreover, histone alterations have a major role in controlling the immune responses in our body (Martino et al., 2011). However, increased histone acetylation at the promoters of pro-inflammatory genes (e.g., TNF-α, IL-1β, IFN-γ) in immune cells leads to sustained transcription of cytokines (Martino et al., 2011; Szyf, 2009). This promotes chronic inflammation, infiltration of autoreactive T-cells into pancreatic islets (Zhang & Dent, 2005; Martino et al., 2011). All these incidents result in inadequate production of insulin, thereby increasing the susceptibility to type 1 diabetes (Feinberg, 2007; Knip et al., 2012).

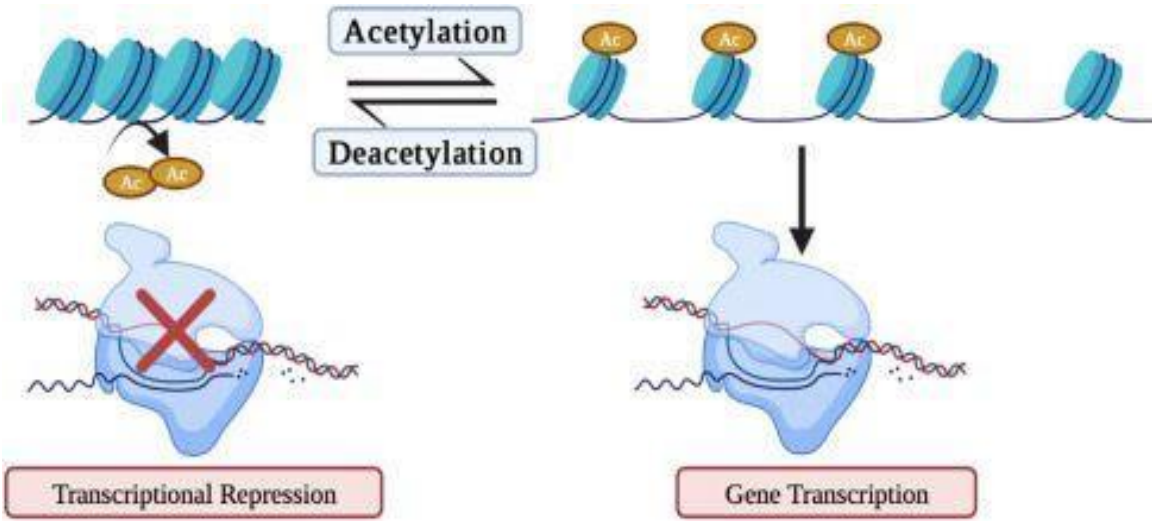

Figure 4: Histone acetylation mechanism (ScienceDirect, 2023).

MicroRNA Dysregulation: MicroRNAs are basically non-coding RNA molecules that crucial for post transcriptional regulation of gene expression by binding to complementary sequences on target mRNAs, causing the inhibition of translation, thus they act as gene silencers (Bartel, 2009; He & Hannon, 2004). However, dysregulated miRNAs such as miR-2, miR-146a, and miR-155 promote inflammatory signalling, impair regulatory T-cell function, and enhance cytokine production (Sebastiani et al., 2022). Again, malfunction of miR-375 may contribute to beta-cell stress and apoptosis (Poy et al., 2009; Latreille et al., 2014). All of these alterations indicate reduced insulin production and are often influenced by environmental stressors, causing the immunological tolerance to deteriorate (Sebastiani et al., 2022; Knip et al., 2012).

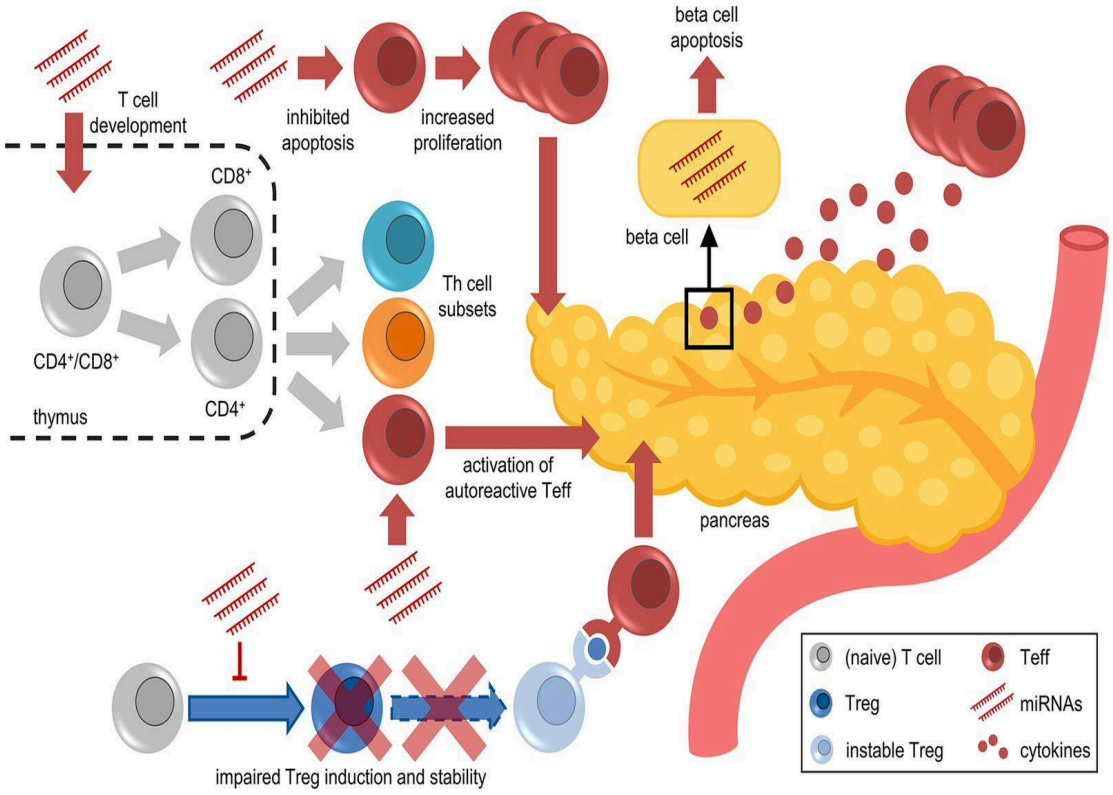

Figure 5: MicroRNA dysregulation in autoimmune diabetes (Sebastiani et al., 2022)

Key Epigenetic Factors Triggering Type 1 Diabetes

The major epigenetic mechanisms discussed previously, that disrupt normal gene regulation and come up with the development of type 1 diabetes and other autoimmune disorders are often triggered or influenced by environmental and biological stressors (Zhao et al., 2006). Some of the major environmental and biological contributors are:

- **Environmental Toxins:** Environmental toxins can be synthetic or naturally occurring compounds that disrupt cellular homeostasis and immune regulation (Kern et al., 2005). Researchers have suggested that environmental toxins don't directly mutate DNA but they alter gene expression through epigenetic mechanisms and elevates the chances of progressing type 1 diabetes (Kern et al., 2005). Some of the major toxins are:
    1. **Heavy Metals :** Arsenic, Cadmium, Lead often found in contaminated water, soil or food (Tchounwou et al., 2012). Exposure to these heavy metals causes chronic inflammation, impaired immune function and autoimmune conditions (Tchounwou et al., 2012).
    2. **Dioxins:** Released in the environment from industrial waste, pesticides, organic pollutants and disrupts histone acetylation, interferes with hormone function and immune regulation (Karmaus et al., 2005).
    3. **Bisphenol A (BPA):** Chemicals present in plastic containers and food packaging (Maffini et al., 2006). BPA has contributed to increased inflammatory responses and immune system disturbances (Maffini et al., 2006).
    4. **Cigarette Smoke:** Cigarette smoke contains over 7000 chemicals including nicotine, formaldehyde, cadmium, carbon monoxide and many more toxins

(Talhout et al., 2011). Promotes chronic inflammation, oxidative stress, metabolic disruption (Lee & Cooke, 2011).

Ingestion, inhalation or dermal contact of environmental toxins play a key part in developing T1D in the human body (Longnecker et al., 2004).

- **Viral Infections:** Enteroviruses such as Coxsackievirus B can cause alteration in the DNA methylation mechanism (Nekoua et al., 2021). This may lead to the activation of proactive T-cells, disruption in immunological tolerance and chronic inflammation (Filippi et al., 2005).
- **Nutritional Deficiencies:** Low levels of vitamin D, Folate, vitamin B12, zinc, selenium, omega-3 fatty acids affect methyl group availability and disturbs DNA methylation process (Mckay et al., 2014).
- **Gut Microbiome Imbalance:** A condition called dysbiosis, characterized by reduced microbial diversity, alters metabolite levels that affect histone acetylation and immune signaling (Belkaid & Hand, 2014).
- **Oxidative Stress:** Causes elevated histone acetylation, inflammatory gene expression alteration, increasing immune cell infiltration (Zhou et al., 2013).
- **Physiological Stress:** Chronic stress leads to elevated levels of cortisol and catecholamines, which increases insulin demand, influences histone modification, miRNA profiles and impair gene regulation (Charmandari et al., 2005). Also influences lifestyle like reduced physical activity, poor dietary choices, All of these increase the chances of developing this condition(Charmandari et al., 2005).

Summarized epigenetic triggers and their outcomes in TD1 are presented in Table 3 (Feinberg, 2007; Knip et al., 2012).

Table 3: Epigenetic triggers and their outcomes in Type 1 Diabetes

TRIGGER	EPIGENETIC IMPACT	OUTCOME
Environmental Toxins	DNA methylation disruption	Autoimmune activation
Viral Infections	CpG methylation changes, microRNA dysfunction	T-cell activation, chronic inflammation
Nutritional Deficiences	Reduced methyl group availability, microRNA dysfunction	Impaired immune tolerance, altered beta-cell survival
Gut Microbiome Imbalance	Histone modification changes, microRNA dysfunction	Altered gut-immune signalling, increased inflammation
Oxidative Stress	Histone acetylation, microRNA dysfunction	Beta-cell apoptosis, elevated cytokine production
Physiological Stress	Histone remodeling, microRNA dysfunction	Altered immune signalling, increased insulin demand
Cigarette Smoke	Global DNA hypomethylation, histone acetylation	Inflammatory gene expression, immune imbalance.

Studies have shown that the number cases of type 1 diabetes have risen drastically in the past 30 years due to increased environmental and biological stressors in the present world (Gale, 2005). Creating awareness and understanding these epigenetic links is crucial for preventive strategies such as improving environmental regulation, promoting detoxification diets, and screening high risk populations (Zhou et al., 2023).

Genetic Contributions to the Onset of type 2 diabetes

This form of diabetes is a persistent metabolic disease caused due to insufficient insulin production or insulin resistance in the body. (Himanshu et al., 2020). The development of this complex condition is a result of a combination of environmental factors, lifestyle, and strong hereditary influences (Laakso & Silva, 2022). According to family and twin studies, genetic influences come up with the development of type 2 diabetes by 25-72% (Laakso & Silva, 2022). Studies have shown that over 130 genetic loci (single nucleotide polymorphisms and gene variants) and molecular mechanisms play a significant character in the growth of type 2 diabetes, as it is a polygenic condition and it is not limited to a single pathway but is a combination of a broad spectrum of biological pathways that influence the secretion of insulin hormone from the beta-cells, insulin sensitivity, overall glucose homeostasis in the body (Majithia & DeForest, 2022). Early diagnosis, risk minimization, and personalized therapeutic strategies to control type 2 diabetes can be possible by proper knowledge, understanding, and awareness about these genetic influences (Ng et al., 2008). Some of the key genetic elements that contribute to the onset of T2D are:

- **TCF7L2:** Also referred to as "Transcription Factor 7-Like 2". It is a highly replicated and strongly associated gene with type 2 diabetes (Ding et al., 2018). The rs7903146 variant of this gene can noticeably reduce the ability of pancreatic cells to respond to glucose which results in inadequate levels of insulin secretion (Villareal et al., 2010). It also negatively affects the action of GLP-1 (glucagon-like peptide-1), a hormone that facilitates blood glucose regulation (Villareal et al., 2010). All of these results in the onset of type 2 diabetes (Sen et al., 2025).

- **IGF2BP2:** Also known as “Insulin-Like Growth Factor 2 mRNA-Binding Protein 2”. It modulates insulin-like growth factor signaling which acts as a RNA-binding protein and influences beta-cell proliferation (Wang et al., 2021). Dysregulation of polymorphisms in this gene has been proved to be linked to obesity and fatty liver, which significantly causes type 2 diabetes (Wittenbecher et al., 2019).
- **PPARG:** Also identified as “Peroxisome Proliferator-Activated Receptor Gamma”. It is a nuclear receptor that regulates adipocyte differentiation where immature cells (preadipocytes) develop into fat-storing cells that facilitates metabolism and insulin sensitivity (Hashemian et al., 2021). The Pro12Ala variant of this gene can improve the body's response to insulin and lowers the risk of T2D (Gouda et al., 2010). However, dysfunction of this gene can cause inflammation in fat-storing tissue and make the body resistant to insulin (Liu et al., 2010).
- **KCNJ11:** Also called “Potassium Inwardly Rectifying Channel Subfamily J Member 11”. This gene regulates a subunit of the ATP-sensitive potassium channel in the beta-cells of pancreas and controls the hormone release (Florez et al., 2007). However, variants of this gene especially E23k disrupts potassium channel function causing defective insulin secretion (Qiu et al., 2014).
- **FTO:** Also identified as “Fat Mass and Obesity-Associated Gene”. This gene can help in energy homeostasis and control appetite (Hertel et al., 2011). Changes in this gene are strongly associated with obesity as it causes increased appetite, fat cell function and lipid metabolism contributing to type 2 diabetes (Kim et al., 2016).
- **IRS1:** Also called “Insulin Receptor Substrate 1”. It works as a key mediator in the insulin signaling cascade in cells so they can take in glucose (Caruso et al., 2014). Polymorphisms in this gene reduces insulin gene activity, causing insulin resistance in

individuals with metabolic syndrome and central obesity (Yousef et al., 2018).

The major genetic variants contributing to the onset of TD2 is summarized in Table 4 (Florez et al., 2007; Sen et al., 2025; Caruso et al., 2014)

Table 4: Major genetic variants contributing to the onset of Type 2 Diabetes

TRIGGER	**GENETIC IMPACT**	**OUTCOME**
TCF7L2	SNPs alter transcriptional regulation of genes involved in insulin secretion and beta-cell function.	Impaired insulin production and increased risk of T2D.
PPARG	Variants like Pro12Ala affect adipocyte differentiation and lipid metabolism.	Reduced insulin sensitivity and increased adiposity.
IGF2BP2	SNPs affect post transcriptional regulation of IGF2.	Impaired beta-cell proliferation.
KCNJ11	Mutations affect ATP-sensitive potassium channels in beta-cells.	Disrupted insulin release and glucose homeostasis.
FTO	SNPs influence energy balance and appetite regulation.	Increased obesity risk, contributing to insulin resistance.
IRS1	Genetic variants impair insulin signaling cascade.	Beta-cell dysfunction and reduced insulin secretion.
SLC30A8	Variants affect zinc transport in beta-cells, essential for insulin crystallization.	Impaired beta-cell proliferation.

- **Other Contributors:** There are many more additional genes such as LCAT (Lecithin-Cholesterol Acyltransferase), APOE (Apolipoprotein E), NOTCH 2, MTNR1B (Melatonin Receptor 1B), SLC30A8 (Zinc Transporter 8) and many more (over 130) affects various pathways, insulin producing beta-cell dysfunction, insulin resistance, glucose intolerance and finally type 2 diabetes onset (Prasad & Groop, 2015).

Epigenetic Influences at the Onset of Type 2 Diabetes:

Epigenetics is basically the study that guides how the inherited changes in gene expression occur or how certain factors can change the way a gene works without altering the foundational gene sequence (Bird, 2007; Moore et al., 2013). Similar to type 1 diabetes, 3 major epigenetic mechanisms which are non-coding RNA regulation, histone modification, and DNA methylation also contribute to the pathogenesis and advancement of type 2 diabetes where DNA methylation silences insulin related genes, causing beta cell dysfunction; histone modification alters chromatin, dysregulates glucose and lipid metabolism; and non-coding RNA disrupts insulin signalling, leading to impaired secretion and uptake (Zhao, 2019; Dayeh, 2014; Volkmar, 2012).

However, various influences can negatively stimulate or affect these chemical modifications such as environmental ,biological stressors, and lifestyle (Barres & Zierath, 2016). Studying these epigenetic factors will not only help in early diagnosis, prevention of the disease, personalized treatment but also open new avenues for therapeutic intervention (Ntarajan et al., 2019; Toperoff et al., 2015).

The below figure shows the gene-diet interaction influencing T2D.

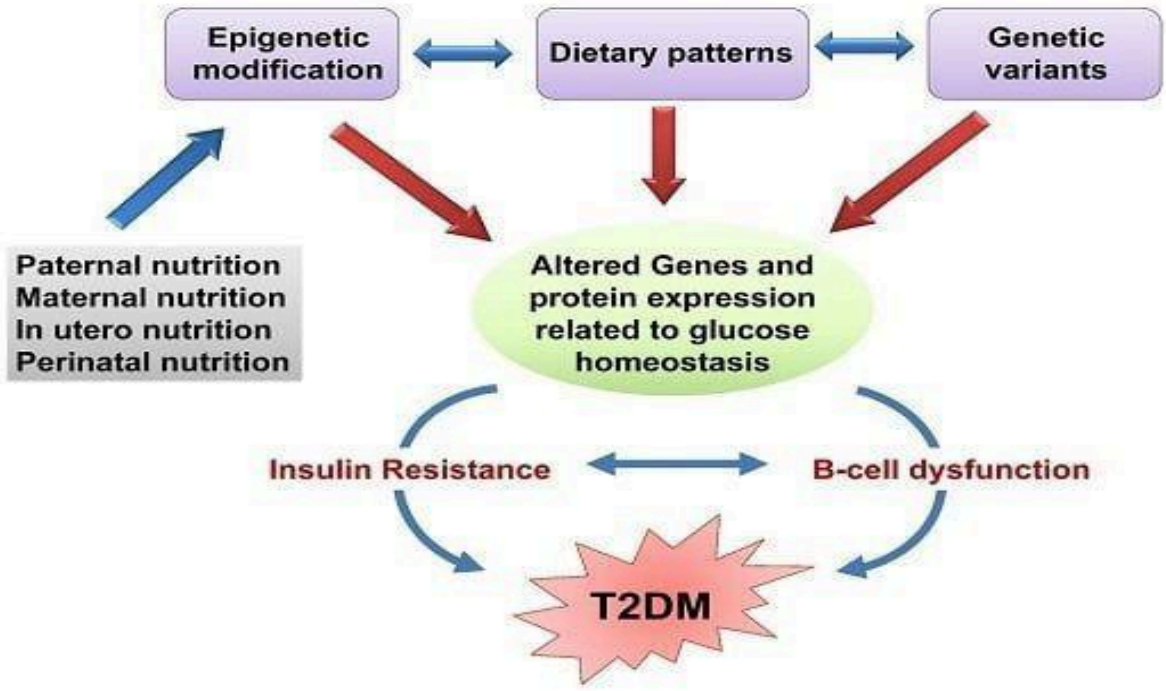

Figure 6: Gene–diet interaction and epigenetic influence in Type 2 Diabetes (Corella & Ordovas, 2017).

Key Epigenetic Factors Triggering Type 2 Diabetes

- **Environmental Exposures:** Getting in contact to environmental toxins and pollutants such as heavy metal (arsenic, lead, cadmium), pesticides, endocrine disrupting chemicals (bisphenol A, phthalates) can stimulate the epigenetic mechanisms and prolonged exposure to these can cause insulin resistance, impaired glucose tolerance, and ultimately T2D (Khan et al., 2016).
- **Physical Inactivity, Diet & Obesity:** Physical inactivity, poor diet (high sugar, saturated fats) are major lifestyle factors contributing to obesity, which is one of the major reasons for type 2 diabetes (Klein et al., 2024; Frouhi, 2023). Less physical movement and

unhealthy diet directly causes obesity and this results in excess adipose tissues, releasing pro-inflammatory cytokines that promote insulin resistance by disrupting normal gene activity (Al-Mansoori et al., 2022).

- **Aging:** As our body ages, cellular mechanisms become less efficient. DNA repair mechanisms weaken, pancreatic beta-cells become less active in producing and secreting insulin, insulin resistance increases, oxidative stress level raises, all of these elevates the risks of type 2 diabetes.
- **Hormonal Fluctuations:** Stress, diet, metabolic state influences the levels of hormones like cortisol, leptin, and insulin in our body (Lucassen & Cizza, 2012). Fluctuation of these hormone levels can alter transcription factors that interact with epigenetic mechanisms, glucose uptake, and fat storage (Xiao et al., 2012; Aronica et al., 2025).
- **Smoking & Alcohol:** Smoking causes high levels of oxidative stress and chronic inflammation in our body (Addisssouky et al., 2024). Nicotine and other harmful chemicals present in cigarettes interfere with insulin signaling and increase blood glucose levels (Bergman et al., 2012). While excessive alcohol consumption impairs liver, pancreatic function and glucose regulation (Yang et al., 2020; Steiner et al., 2015).
- **Sleep & Stress:** Sleep deprivation and chronic stress leads to elevated cortisol levels, decreases insulin sensitivity, increases appetite, promotes weight gain resulting in persistent hyperglycemia (Che et al., 2021; Lucassen & Cizza, 2012).
- **Socioeconomic Factors:** Poor access to healthy diet, healthcare facilities and education can indirectly affect epigenetic regulation (Jiao, 2024; Affret et al., 2017). Moreover, financial instability causes chronic stress, deprived sleep, unhealthy lifestyle and even drug addiction which lead to biological changes that elevates the diabetes development risks (Crielaard et al., 2021; Darku & Diyaolu, 2024).

The epigenetic factors influencing epigenetic regulation of TD2 is given in Table 5 (Jiao, 2024; Affret et al., 2017; Crielaard et al., 2021; Darku & Diyaolu, 2024).

Table 5: Epigenetic factors influencing regulation of Type 2 Diabetes

TRIGGER	**EPIGENETIC IMPACT**	**OUTCOME**
Environmental Exposure	Pollutants (e.g., BPA, heavy metals) alter DNA methylation and histone acetylation in metabolic genes.	Disrupted insulin signaling, increased inflammation, and beta-cell dysfunction.
Physical Inactivity, Diet, and Obesity	High-fat diets and sedentary behavior modify methylation of insulin related genes and inflammatory cytokines.	Promotes insulin resistance, chronic inflammation, and metabolic imbalance.
Aging	Global hypomethylation and site-specific hypermethylation in pancreatic and muscle tissue.	Impaired beta-cell function and reduced insulin sensitivity.
Hormonal Fluctuation	Alters histone modifications and miRNA expression in insulin-regulating pathways.	Dysregulated glucose metabolism and increased T2D susceptibility.
Sleep and Stress	Chronic sleep deprivation and psychological stress dysregulate cortisol levels, miRNA profiles, histone acetylation.	Impaired glucose metabolism, increased insulin resistance and beta-cell exhaustion.
Socioeconomic	Low income, poor education, and limited	Elevated risk of T2D via

Factors	healthcare access influence lifestyle-driven epigenetic changes.	cumulative stress, metabolic disruption, and inflammation.
Smoking and Alcohol	Induces oxidative stress and modifies DNA methylation histone acetylation in metabolic tissues.	Promotes insulin resistance, inflammation, and beta-cell apoptosis.

The genesis and advancement of T2D is not only a result of genetic influences but also environmental effects, biological stressors and lifestyle choices (Kolb & Martin, 2017; Franks et al., 2013). Understanding the interplay between these factors will open new doors in disease management, improving the quality of life, and reducing the global burden of T2D (Amin, 2022; Jazieh et al., 2024).

1.5 Comparative overview of Type 1 and Type 2 Diabetes Mellitus

A summarized comparison between TD1 and TD2 presented in Table 6 (Khan et al., 2016; Kolb & Martin, 2017; Zhang & Dent, 2005; Martino et al., 2011; Ahmed et al., 2020)

Table 6: Comparative overview of Type 1 and Type 2 Diabetes Mellitus

ASPECT	**TYPE 1 DIABETES**	**TYPE 2 DIABETES**
Etiology	Autoimmune destruction of pancreatic beta-cells.	Insulin resistance, beta-cell destruction.
Onset Age	Common in children, adolescents, and adults.	Typically in adults and older individuals.

Prevalence	~5-10% of global cases.	～90-95% of global cases.
Insulin Status	Absolute insulin deficiency .	Relative insulin deficiency.
Genetic Influence	Strong HLA-linked autoimmune susceptibility.	Polygenic involves metabolic, hormonal, adipocyte related genes.
Key Gene	HLA-DR, HLA-DQ, INS, PTPN22, CTLA, IL2RA.	TCFL2, PPARG, FTO, KCNJ11, IGF2BP2, IRS1, SLC30A8
Epigenetic Mechanisms	DNA methylation, histone modification, microRNA dysregulation	Epigenetic changes affecting insulin signalling, lipid metabolism, beta-cell function.
Environmental Triggers	Viral infections, toxins, nutritional deficiencies, stress	Obesity, poor diet, aging, hormonal imbalance, socioeconomic stress.
Symptoms	Rapid onset: Polyuria, polydipsia, weight loss, fatigue	Gradual onset: fatigue, neuropathy, slow wound healing, edema
Management Focus	Lifelong insulin therapy, autoimmune modulation.	Lifestyle modification,oral insulin (if needed).
Preventability	Limited; mostly non preventable.	Largely preventable.
Complication Risk	High if untreated: ketoacidosis, organ damage.	High if unmanaged: cardiovascular, renal complication.

Chapter 2

Clinical Implications:

The raising knowledge and understanding about the connection between the hereditary and epigenetic influences contributing in the progression of diabetes mellitus is reforming clinical strategies to deal with it (Dhawan & Natarajan, 2019). It is showing new exciting possibilities in healthcare, enhancing the quality of life (Jazieh et al., 2024). By expressing these molecular insights into actionable approaches, healthcare professionals now can predict who's at risk by early detection, tailor personalized treatment for every individual, and explore new preventive ways (Singh et al., 2025; Niger et al., 2024). By bridging molecular science with healthcare, we are moving closer to more personalized, effective and proactive diabetic care which is smarter, safer, and more effective (Dhieb et al., 2025; Malandrino & Smith, 2011).

2.1 The Study's Objective

The study's main goal is to investigate and comprehensively explore and analyze how both genetic and epigenetic variables play a role in causing diabetes mellitus with the objective of understanding how inherited variations and environmentally influenced patterns influence disease susceptibility, progression, and potential therapeutic targets (Ahmed et al., 2020; Barres & Zierath, 2016). This study seeks to examine how inherited genetic variants, such as single nucleotide polymorphisms and gene mutations influence the onset of diabetes (Cheng et al., 2025). Additionally, it targets to explore epigenetic modifications- including DNA methylation, histone alteration, and non-coding RNA activities, that regulate gene expression in response to environmental & lifestyle factors (Bird, 2007; Bartel, 2009).

By studying these two types of factors together, this project hopes to better understand why some people develop diabetes while others don't, even if they have similar habits or environments. This knowledge might help in finding improved strategies for future prevention, diagnosis, and treatment of diabetes.

Chapter 3

Methodology:

This review-based study was conducted to explore and synthesize the genetic and epigenetic involvement in the initiation and escalation of diabetes mellitus,while emphasizing on both type 1 and 2 diabetes. Well structured and organized approaches and strategies were adopted to ensure systematic identification, critical evaluation and synthesis relevant literature from high impact peer-reviewed sources to ensure academic rigor and transparency that covers the involved all the hereditary factors, molecular pathways, genetic and environmental interaction, lifestyle influences and regulatory mechanisms underlying diabetes mellitus.

- **Study Design**

A concept driven narrative literature was employed, aimed at evaluating, synthesizing and organizing current knowledge and information about the genetic and epigenetic determinants of diabetes mellitus. The study design was selected to allow comprehensive coverage and accommodate the multifactorial nature, diverse molecular mechanisms and regulatory pathways involved to this disorder. Instead of relying on rigid systemic protocol, in order to facilitate qualitative analysis and mechanistic investigations while maintaining methodological rigor, this design allowed for the inclusion of diverse and broader range of study types.

- **Literature Identification**

A targeted and comprehensive search was conducted across the major biomedical databases especially in Pubmed for biomedical and molecular genetic search, Google Scholar for broader access to supplementary sources, ScienceDirect and Scopus for high impact journals. The research was performed between July and August of 2025. Most of the targeted articles were published from 2015 to 2025 though some additional articles were studied to get detailed information and depth knowledge which were published even before the year 2000. The search strategy incorporated both keywords and controlled vocabulary, including:

1. “Diabetes Mellitus” OR “diabetes classification”
2. “Type 1 diabetes” OR “Type 1 diabetes”
3. “Diabetes Mellitus” AND “genetic variants”
4. “Diabetes mellitus” AND “epigenetic regulations”
5. “DNA methylation”
6. “Histone modification”
7. “Non-coding RNAs”
8. “Insulin resistance”
9. “Diabetes mellitus” AND “preventive care”
10. “Diabetes mellitus” AND “Gene-environment interaction”

Boolean operators (AND, OR) are used to filter the search and ensure relevance to the studies concept.

- **Screening and Eligibility**

After completing some initial search across the websites some relevant articles were filtered and chosen. Articles were screened and filtered through a three step process: title review, abstract screening, and full text availability. Articles were included to the further evaluation list if they focused on human subjects with TD1 and TD2, investigated allelic variants, epigenetic mechanisms and influences. Only peer-reviewed and employing validated articles written in English were considered. Exclusion criteria included animal studies, in-accessible full text, non-english publications and articles lacking primary data. Highly eligible articles were chosen for thematic synthesis.

- **Data Extraction and Organization**

Eligible articles and studies were reviewed very sincerely. Relevant data were extracted from each selected study using a structured template to support thematic analysis, Key information included study title, publication year, authors, the type of diabetes investigated, genetic and epigenetic targets, study population, their characteristics, sample size, and methodological approaches. Collected information was categorized into different sectors reflecting core disease mechanisms, disease symptoms, genetic susceptibility, epigenetic regulations, beta-cell dysfunction, insulin resistance and preventive options. This structured organization enabled comparative analysis across studies and helped identify consistent molecular patterns, emerging biomarkers and gaps in current research.

- **Quality Assessment:**

To ensure accurate information and proper relevance, each study was evaluated for methodological rigor, sample representativeness, and reproducibility findings. Priority was given

to studies with robust and elaborated information, adequate controls, and validated analytical techniques. Studies were also evaluated for transparency in reporting, ethical approval and reproducibility of findings. The rigorous filtering process ensured that only methodologically sound and contextually relevant studies contribute to the synthesis of findings.

- **Ethical Considerations:**

Since secondary data from published literature forms the basis of the study, all the articles included were screened for ethical compliance with special care to ensure that the original researchers had upheld participants confidentially and data protection measures were taken according to international guidelines. Moreover, academic integrity was strictly followed through accurate citations, avoidance of plagiarism and respectful representation of original findings.

- **Limitations:**

Despite efforts to ensure methodological rigor, this review is subjected to several limitations including potential publication bias, heterogeneity in study design, exclusion of non-English articles and unpublished or non-authorized data. Variability in genetic backgrounds across populations may also influence the basic findings.

Chapter 4

Discussion:

The research study reinforces diabetes mellitus as a complex metabolic disease which is developed due to the influences of both genetic predisposition and epigenetic regulations. Type 1 diabetes, which is highly driven by the genetic elements, mistakenly attacks insulin producing pancreatic cells and destroys them and leads to diabetes. Moreover, epigenetic mechanisms and

changes highly influence the genetic elements, helping in the disease onset and development. Although, misregulation in epigenetic mechanisms associate the negative lifestyle factors and hereditary risks, moving the body towards type 2 diabetes development. So, studying both the underlying genetic and epigenetic influences is the only option for inventing treatments and preventive techniques of diabetes mellitus.

Chapter 5

Conclusion:

Diabetes mellitus has become one of the fastest growing diseases in today's world affecting hundreds and thousands of people across the world. Also it doesn't follow any age range, while young adults, adolescents and even children are having type 1 diabetes, type 2 is mostly seen in aged and older groups of people. Moreover, if it is not controlled, it influences a wide range of other complications in the body such as kidney failure, renal failure, cardiovascular , neuronal, ophthalmic and dental problems. The most alarming news is that there is no treatment to cure diabetes mellitus permanently. So it is very important to prevent diabetes before it can develop in our body and the prevention lies in our lifestyle. Maintaining a proper diet, reducing the sources of carbs, exercising regularly, losing extra weight, quitting smoking and alcohol can be really helpful in prediabatic conditions. In the diabetic state maintaining a proper lifestyle with proper medication is a must. Having regular doctor check-up, proper medications, regular blood glucose level checks, proper diet, physical activity, foot care are some of the rules that should be followed strictly by a diabetic patient to raise the standard of living. As diabetes has become a healthcare challenge, researchers all over the world are working efficiently to move towards a positive future.

References:

Ahmed, S. A. H., Ansari, S. A., Mensah-Brown, E. P. K., & Emerald, B. S. (2020). The role of DNA methylation in the pathogenesis of type 2 diabetes mellitus. Clinical Epigenetics, 12(1), 104. https://doi.org/10.1186/s13148-020-00896-4

American Diabetes Association. (2024). Standards of medical care in diabetes—2024. Diabetes Care, 47(Suppl. 1). https://doi.org/10.2337/dc24-S001

Ashcroft, F. M., & Rorsman, P. (2012). Diabetes mellitus and the β-cell: The last ten years. Cell, 148(6), 1160–1171. https://doi.org/10.1016/j.cell.2012.02.010

Aubin, A.-M., Cattan, P., Lehuen, A., & Diana, J. (2022). The NOD mouse beyond autoimmune diabetes. Frontiers in Immunology, 13, Article 874769. https://doi.org/10.3389/fimmu.2022.874769

Barrès, R., & Zierath, J. R. (2016). The role of nutrition and exercise in the regulation of the epigenome and its implications for metabolic disease. Nature Reviews Endocrinology, 12(11), 563–571. https://doi.org/10.1038/nrendo.2016.114

Bartel, D. P. (2009). MicroRNAs: Target recognition and regulatory functions. Cell, 136(2), 215–233. https://doi.org/10.1016/j.cell.2009.01.002

Berg, J. M., Tymoczko, J. L., & Stryer, L. (2002). Biochemistry (5th ed.). W. H. Freeman.https://www.ncbi.nlm.nih.gov/books/NBK22528/

Bird, A. (2007). Perceptions of epigenetics. Nature, 447(7143), 396–398. https://doi.org/10.1038/nature05913

Brady, S., Smith, J., Johnson, L., Patel, R., & Williams, T. (2022). Clinical manifestations of type 2 diabetes. Journal of Clinical Endocrinology, 107(3), 456–462. https://doi.org/10.1210/clinem/dgac123

Brady, V., Thompson, K., Miller, D., & Roberts, H. (2022). Characterization of symptoms and symptom clusters for type 2 diabetes. Diabetes Spectrum, 35(2), 159–170. https://doi.org/10.2337/ds21-0045

Campbell-Thompson, M. L., Wasserfall, C., Kaddis, J., & Atkinson, M. A. (2013). The diagnosis of insulitis in human type 1 diabetes. Diabetologia, 56(11), 2541–2543. https://doi.org/10.1007/s00125-013-3043-5

Centers for Disease Control and Prevention. (2022). Diabetes and insulin production and function [Infographic]. CDC. https://www.cdc.gov/diabetes/library/socialmedia/infographics.html

Chen, X., Zhang, L., & Chen, W. (2025). Global, regional, and national burdens of type 1 and type 2 diabetes mellitus in adolescents from 1990 to 2021, with forecasts to 2030. BMC Medicine, 23, Article 48. https://doi.org/10.1186/s12916-025-03890-w

Cheng, Y., Li, H., Wang, J., Zhao, P., & Liu, Q. (2025). Genetic susceptibility and environmental triggers in diabetes. Journal of Endocrinology, 256(1), 1–15. https://doi.org/10.1530/JOE-25-0318

Corella, D., & Ordovás, J. M. (2017). Gene–diet interactions in type 2 diabetes: The chicken and egg debate. International Journal of Molecular Sciences, 18(6), 1188. https://doi.org/10.3390/ijms18061188

Craig, M. E., Jefferies, C., Dabelea, D., Balde, N., Seth, A., & Donaghue, K. C. (2020). Epidemiology of type 1 diabetes. Diabetes Research and Clinical Practice, 159, 107919. https://doi.org/10.1016/j.diabres.2019.107919

Damiano, G., Rinaldi, R., Raucci, A., Molinari, C., Sforza, A., Pirola, S., Paneni, F., Genovese, S., Pompilio, G., & Vinci, M. C. (2024). Epigenetic mechanisms in cardiovascular complications of diabetes: Towards future therapies. Molecular Medicine, 30, Article 161. https://doi.org/10.1186/s10020-024-00939-z

Dayeh, T., & Ling, C. (2015). Does epigenetic dysregulation of pancreatic islets contribute to impaired insulin secretion in type 2 diabetes? Biochemical Society Transactions, 43(2), 323–327. https://doi.org/10.1042/BST20140302

DeFronzo, R. A., Ferrannini, E., Groop, L., Henry, R. R., Herman, W. H., Holst, J. J., Hu, F. B., Kahn, C. R., Raz, I., Shulman, G. I., Simonson, D. C., Testa, M. A., & Weiss, R. (2015). Pathogenesis of type 2 diabetes mellitus. Diabetes Care, 38(8), 1552–1561. https://doi.org/10.2337/dc15-0142

Dhawan, S., & Natarajan, R. (2019). Epigenetics and type 2 diabetes risk. Current Diabetes Reports, 19(8), Article 47. https://doi.org/10.1007/s11892-019-1168-8

Drivsholm, T., Nielsen, B., Olivarius, N. D. F., Siersma, V., & Hollnagel, H. (2005). Symptoms, signs and complications in newly diagnosed diabetic patients. Diabetes Research and Clinical Practice, 68(2), 130–139. https://doi.org/10.1016/j.diabres.2004.09.004

Esser, N., Utzschneider, K. M., & Kahn, S. E. (2020). Early beta cell dysfunction vs insulin hypersecretion in dysglycaemia pathogenesis. Diabetologia, 63(10), 2007–2021. https://doi.org/10.1007/s00125-020-05245-x

Galindo, R. J., Aleppo, G., Klonoff, D. C., Bergenstal, R. M., & Garg, S. K. (2023). Personalized diabetes care. Journal of Diabetes Science and Technology, 17(2), 345–356. https://doi.org/10.1177/19322968221123456

Galindo, R. J., Aleppo, G., Klonoff, D. C., Bergenstal, R. M., & Garg, S. K. (2023). IDegLira vs. basal-bolus insulin in poorly controlled type 2 diabetes. Diabetes Care, 46(9), 1640–1645. https://doi.org/10.2337/dc22-1234

Greenbaum, C. J., Anderson, M. S., Bluestone, J. A., Burren, O., Ehlers, M., Gottlieb, P. A., Herold, K. C., Long, S. A., Pociot, F., & Todd, J. A. (2025). Genetic risk and progression of type 1 diabetes. Nature Reviews Endocrinology. Advance online publication. https://doi.org/10.1038/s41574-025-00890-5

Harding, J. L., Wander, P. L., Zheng, Y., Narayan, K. M. V., & Gregg, E. W. (2022). The incidence of adult-onset type 1 diabetes: A systematic review. Diabetes Care, 45(4), 994–1006. https://doi.org/10.2337/dc21-1234

Hill-Briggs, F., Adler, N. E., Berkowitz, S. A., Chin, M. H., Gary-Webb, T. L., Navas-Acien, A., Thornton, P. L., & Haire-Joshu, D. (2021). Social determinants of health and diabetes: A scientific review. Diabetes Care, 44(1), 258–279. https://doi.org/10.2337/dci20-0053

Hu, F. B. (2011). Globalization of diabetes: The role of diet, lifestyle, and genes. Diabetes Care, 34(6), 1249–1257. https://doi.org/10.2337/dc11-0442

Huang, G., Cheng, J., Li, Y., Wang, X., Zhang, Y., & Zhao, L. (2025). Association of P2X7 polymorphisms with type 2 diabetes susceptibility and complications. PLOS ONE, 20(1), e0318134. https://doi.org/10.1371/journal.pone.0318134

Jazieh, A. R., Alsaud, A. W., Alkattan, K., Sabbah, B. N., Arabi, T. Z., Asim, Z., & Yaqinuddin, A. (2024). Diabetes: Recent advances and future perspectives. Biomedicines, 12(12), Article 2875. https://doi.org/10.3390/biomedicines12122875

Kahn, S. E., Hull, R. L., & Utzschneider, K. M. (2006). Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature, 444(7121), 840–846. https://doi.org/10.1038/nature05482

Knip, M., Veijola, R., Virtanen, S. M., Hyöty, H., Vaarala, O., & Åkerblom, H. K. (2005). Environmental triggers and determinants of type 1 diabetes. Diabetes, 54(Suppl. 2), S125–S136. https://doi.org/10.2337/diabetes.54.suppl_2.s125

Kolb, H., & Martin, S. (2017). Environmental/lifestyle factors in the pathogenesis and prevention of type 2 diabetes. BMC Medicine, 15, Article 131. https://doi.org/10.1186/s12916-017-0901-x

Malandrino, N., & Smith, R. J. (2011). Epigenetics and diabetes risk: Not just for imprinting anymore? Diabetes, 60(7), 1859–1860. https://doi.org/10.2337/db11-0460

Park, S. Y., Gautier, J. F., & Chon, S. (2021). Assessment of insulin secretion and insulin resistance in humans. Diabetes & Metabolism Journal, 45(5), 641–654. https://doi.org/10.4093/dmj.2021.0220

Patterson, C. C., Karuranga, S., Salpea, P., Saeedi, P., Dahlquist, G., Soltesz, G., Ogle, G. D., & Silink, M. (2019). Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents. Diabetes Research and Clinical Practice, 157, 107842. https://doi.org/10.1016/j.diabres.2019.107842

Petersdorf, E. W., & Gutierrez-Arcelus, M. (2023). Single-cell eQTL mapping of classical HLA genes in immune cells. Nature Genetics, 55(6), 897–906. https://doi.org/10.1038/s41588-023-01385-2

Reddy, M. A., Zhang, E., & Natarajan, R. (2015). Epigenetic mechanisms in diabetic complications and metabolic memory. Diabetologia, 58, 443–455. https://doi.org/10.1007/s00125-014-3462-y

Richards, S. E., Wijeweera, C., & Wijeweera, A. (2022). Lifestyle and socioeconomic determinants of diabetes: Evidence from country-level data. PLOS ONE, 17(7), e0270476. https://doi.org/10.1371/journal.pone.0270476

Rosen, E. D., Kaestner, K. H., Natarajan, R., Patti, M. E., Sallari, R., Sander, M., & Susztak, K. (2018). Epigenetics and epigenomics: Implications for diabetes and obesity. Diabetes, 67(10), 1923–1931. https://doi.org/10.2337/db18-0356

Siddiqui, K., George, T. P., Joy, S. S., & Alfadda, A. A. (2022). Risk factors of chronic kidney disease among type 2 diabetic patients with longer duration of diabetes. Frontiers in Endocrinology, 13, Article 1079725. https://doi.org/10.3389/fendo.2022.1079725

Singh, O., Verma, M., Dahiya, N., Senapati, S., Kakkar, R., & Kalra, S. (2025). Integrating polygenic risk scores for personalized diabetes care. Diabetes Therapy, 16, 149–168. https://doi.org/10.1007/s13300-024-01676-6

Stankov, K., Benc, D., & Draskovic, D. (2013). Genetic and epigenetic factors in etiology of diabetes mellitus. World Journal of Diabetes, 4(6), 115–123. https://doi.org/10.4239/wjd.v4.i6.115

Templeman, E. L., Sharp, S. A., Weedon, M. N., & Hattersley, A. T. (2025). Development and recalibration of a multivariable type 1 diabetes prediction model. BMC Medicine, 23, Article 433. https://doi.org/10.1186/s12916-025-0433-y

Tosur, M., Onengut-Gumuscu, S., & Redondo, M. J. (2025). Type 1 diabetes genetic risk scores: History, application and future directions. Current Diabetes Reports, 25, Article 22. https://doi.org/10.1007/s11892-025-01575-5

Vafiadis, P., Bennett, S. T., Todd, J. A., Nadeau, J., Grabs, R., Goodyer, C. G., & Polychronakos, C. (1997). Insulin expression in the human thymus is modulated by INS VNTR alleles at the IDDM2 locus. Nature Genetics, 15, 289–292. https://doi.org/10.1038/ng0397-289

Weir, G. C., & Bonner-Weir, S. (2004). Five stages of evolving beta-cell dysfunction in the pathogenesis of type 2 diabetes. Diabetes, 53(Suppl. 3), S16–S21. https://doi.org/10.2337/diabetes.53.suppl_3.s16

Yu, Y., Vetere, P., Goobie, G., & Rabi, D. (2013, July 11). Pathogenesis of diabetes mellitus (DM), type II [Medical diagram]. The Calgary Guide. https://www.thecalgaryguide.com/pathogenesis-of-diabetes-mellitus-type-ii/

Zhou, Z., & Bluestone, J. A. (2015). miRNA regulation of T-cell development and autoimmunity. Nature Reviews Immunology, 15(5), 317–330. https://doi.org/10.1038/nri3832