



Contents lists available: [Bio-Research](#)  
Journal of Biological Research and Biotechnology

journal homepage: <https://www.bio-research.com.ng> and  
<https://www.ajol.info/index.php/br/about>



## Biological Risk Factors of Type 1 Diabetes Mellitus (T1DM) in Iraqi Pediatric and Adolescent Populations within a Global Context: A Comparative Review



Israa M. Ali Alameen<sup>1\*</sup>, Sumayah Mahmood Rafid<sup>1</sup>, Farah Ali Hameed<sup>2</sup>

<sup>1</sup>Department of community health techniques, Institute of Medical Technology/ Baghdad , Middle Technical University, Baghdad, Iraq.

<sup>2</sup>Department of Emergency medicine and first aids Techniques, Institute of Medical Technology/ Baghdad , Middle Technical University, Baghdad, Iraq.

Israa M. Ali Alameen; [israa.m.ali.alamee@gmail.com](mailto:israa.m.ali.alamee@gmail.com)\*, Sumayah Mahmood Rafid; [sumayahrafid@gmail.com](mailto:sumayahrafid@gmail.com) , Farah Ali Hameed; [farah\\_ali3@mtu.edu.iq](mailto:farah_ali3@mtu.edu.iq)

Received: 10<sup>th</sup> November 2025 / Accepted: 10<sup>th</sup> December 2025 / **Published Online: 15<sup>th</sup> February, 2026**

© The Author(s), under exclusive license to Bio-Research-Journal-of-Biological-Research-and-Biotechnology, 2025

DOI: <https://dx.doi.org/10.4314/br.v23i3.1>

### Abstract

Type 1 Diabetes Mellitus (T1DM) is considered a chronic autoimmune disease which affects children mainly due to the destruction of beta cells of the islets of Langerhans of the pancreas. This review aims to summarize the biological risk factors—genetic, autoimmune, and viral—affecting Iraqi children, and to identify research gaps for future studies. A narrative comparative review of studies was conducted in Iraq between 2014 and 2025 and systematically compared them with selected global research. The global studies included primarily genetic and immunological case-control and cross-sectional investigations on pediatric and adolescent populations with Type 1 Diabetes Mellitus (T1DM). This approach enabled the comparison of molecular and immunological findings between local and international data. The review focused on biological risk factors such as genetic markers (e.g., HLA-DR3/DR4, INSR, CTLA4, PTPN22, IL2RA, TYK2), autoantibodies, and viral triggers associated with T1DM. Comparative analysis revealed that Iraqi studies demonstrated significant genetic associations of Type 1 Diabetes Mellitus (T1DM) with HLA-DR3/DR4, INSR, CTLA4, and PTPN22 variants, consistent with patterns observed in global research. Other genes such as IL2RA, INS (VNTR), IFIH1, TYK2, ERBB3, and CLEC16A showed variable or limited evidence, reflecting gaps in local investigation compared with international findings. Elevated autoantibody levels and Coxsackie B virus infection were also identified as major immunological and viral triggers, confirming the multifactorial and globally comparable nature of T1DM involving genetic, immune, and environmental factors. These findings underscore Iraq's limited genetic coverage compared to international standards and emphasize the need for integrative, large-scale research. The comparative analysis revealed that while Iraqi studies have identified key genetic and immunological determinants of Type 1 Diabetes Mellitus (T1DM) in children and adolescents, their methodological scope and molecular coverage remain limited compared to international standards. Addressing these disparities requires large-scale, multi-center studies integrating global techniques and datasets to strengthen local understanding, early detection, and personalized diabetes care in Iraq.

**Keywords:** Type 1 Diabetes Mellitus (T1DM), Genetic and immunological risk factors, Pediatric and adolescent populations.

### Introduction

Diabetes Mellitus (DM) is one of the most common chronic conditions worldwide. It ranks amongst the top leading causes of mortality around the world, with about 589 million adults suffering from diabetes currently (IDF, 2025), and about 1.2 million children and adolescents (Magliano et al., 2021). The incidence of the disease is steadily increasing from the last decades, particularly

among children and adolescents according (IDF, 2021 studies done in Low- and middle-income countries revealed that the lack of health awareness and inadequate healthcare infrastructure play a key role in the rise of newly diagnosed diabetes cases (Ogle et al., 2023). Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is generally classified into (T1DM), (T2DM), and secondary

DOI: <https://dx.doi.org/10.4314/br.v23i3.1>

forms. T1DM, an autoimmune disease, primarily affects children and adolescents due to the destruction of pancreatic  $\beta$ -cells, leading to absolute insulin deficiency (Antar et al., 2023). Globally, its prevalence is steadily increasing, particularly in low- and middle-income countries, where limited awareness and insufficient healthcare infrastructure contribute to the rise in newly diagnosed cases (Hossain et al., 2024). Considering the global burden, this review focuses on Iraqi children and adolescents, the most vulnerable age groups, and aims to summarize biological and immunological risk factors influencing the onset and progression of T1DM (Hammoud et al., 2023). Considering the historical background of the disease and its steadily increasing prevalence among all age groups, children (under 15 years) and adolescents (15-19 years) are the most vulnerable age groups (Hossain et al., 2024). "Understanding the unique biological determinants of T1DM in these age groups is therefore critical for prevention and early management. In children and adolescents, (T1DM) is the most common (T1DM). In this type of diabetes, the beta cells are completely destroyed, resulting to no insulin production (Lucier & Mathias, 2024). In children and adolescents, (T1DM) is the most common type of diabetes mellitus. In this type, pancreatic beta cells are completely destroyed, leading to absolute insulin deficiency and lifelong dependence on insulin therapy. Managing diabetes in children is particularly challenging because their bodies are still developing, making disease control more complex. Managing diabetes in children is particularly challenging because their bodies are still developing, making disease control more complex. (Lee et al., 2024). The most common complications of (T1DM) in children include kidney damage, diabetic retinopathy or blindness, and growth retardation. This growth delay is primarily attributed to insulin deficiency, as insulin acts not only as a metabolic hormone but also as an anabolic and growth-promoting factor essential for normal physical development, (Alsharairi, 2024). Early diagnosis of the disease helps to protect children and adolescents (under 19 years of age) with (T1DM) and reduce its impact. Therefore, these children should be prioritized in terms of early screening, continuous education, and awareness—especially for parents and their social and school environments—in order to mitigate long-term effects and improve the quality of life for this group (Thomas & Ng, 2020).

In addition to the challenges mentioned above, Iraqi children and adolescents face further complex difficulties due to limited healthcare resources and insufficient national data. Although the number of affected cases is increasing, there remains a lack of accurate statistics, early screening programs in schools, and effective media awareness initiatives. These factors collectively delay disease diagnosis and contribute to increased suffering among young patients. Although the number of affected children and adolescents is increasing, we still face a lack of accurate statistics in Iraq, early screening programs in schools, and media awareness initiatives. ...These factors collectively delay disease diagnosis and contribute to increased suffering among young patients (Scaccia, 2025).

In addition to the limited resources and delayed diagnosis, multiple risk factors contribute to the rising incidence of (T1DM) among Iraqi children and adolescents. These include genetic susceptibility (such as HLA and CTLA-4 polymorphisms), autoimmune reactions targeting pancreatic  $\beta$ -cells, and potential viral or environmental triggers that have been reported in global studies but remain underexplored in Iraq. A targeted literature search across PubMed, Scopus, and Google Scholar revealed that previous Iraqi publications on (T1DM) have addressed isolated domains — such as HLA genotypes, CTLA-4 polymorphism, or immune markers — without integrating these biological determinants into a unified analytical framework. To the best of our knowledge, no prior Iraqi review has systematically examined genetic, immunological, and viral contributors together. This review therefore provides the first comprehensive synthesis of these biological factors in Iraqi children and adolescents, highlighting key national research gaps within a global context. For example, some papers have examined biological factors related to a specific age group, but significant gaps still exist that directly affect the possibility of effective disease management — such as the absence of early screening in health centers, the lack of necessary awareness programs in schools, and poor coordination between the health and education sectors (Sawyer et al., 2022). We can see here that there is a strong and urgent need for comprehensive reviews that combine what has already been addressed and what has not yet been tackled, in order to identify existing shortcomings and gaps, and consequently work on improving them. Building on this perspective, this review adopts a comparative analytical approach that contrasts findings from Iraqi studies with international research on genetic, immunological, and viral determinants of (T1DM). This approach helps identify both overlapping mechanisms and unique research gaps within the Iraqi pediatric and adolescent context compared to global evidence. In line with this objective, this review focus on one of the four main topics that have a direct impact on individuals with (T1DM), and this effect has an influence observed in children and adolescent. the first one is the biological factors, including (genetic and immune-related components) Ries (2023), and the institutional role is considered (Scaccia et al., 2025), This study aims to identify and analyze the main biological determinants of (T1DM), including genetic, immunological, and viral factors, that contribute to the development and progression of the disease in children and adolescents in Iraq. The importance of this study lies in its efforts to understand the genetic, immunological, and viral mechanisms underlying the disease, to clarify its pathogenesis and explain differences between population groups. It also aims to support the establishment of national genetic databases that will contribute to the development of future studies. It also aims to assist in the early detection of individuals at higher risk, enable targeted prevention, and develop more accurate and effective personalized treatments. By comparing national data with global studies, this review aims to address existing national research gaps within genetic, immunological, and viral domains, and to compare local evidence in Iraqi child population with global data.

## Materials and Methods

### Research design

This review adopted a narrative comparative analysis approach to collect and evaluate the studies concerning (T1DM) in children and adolescents, particularly in Baghdad city.

### Search Strategy

An in-depth search was conducted using several scientific databases, including PubMed, Scopus, Google Scholar, and Web of Science. The following keywords were used: Type 1 Diabetes, T1DM, children, adolescents, Baghdad, Iraq, biological risk factors, early screening, and institutional gaps. In addition, selected global studies focusing on genetic, immunological, and viral determinants of T1DM were reviewed for comparative analysis.

### Selection Criteria

Articles published between 2014 to 2025 focused on children and adolescent T1DM studies in Iraq. Studies focused on T1DM in adult populations or T2DM were not included in the study.

### Data Extraction and Analysis

A qualitative analysis was conducted to identify scientific gaps in Iraqi studies related to genetic, immunological, and institutional factors influencing (T1DM), and propose context-specific solutions that align with available national resources.

## Results

### Biological factors

The biological factors such as genetic predisposition, immune dysregulation, and viral infections, play a significant role in the progression of (T1DM) in children and adolescents. The most prevalent factors which affects this group of patients are genetic predisposition, and immune-related dysfunctions, and viral infections that may trigger the body to attack its own cells (Kumar et al., 2025).

### Genetic Factors

In exploring the biological factors contributing to the development of T1DM, genetic predisposition remains a central focus, especially in children and adolescents. In this review, we focused on immunity-related genes and their single nucleotide polymorphisms (SNPs), which are known to influence susceptibility to (T1DM) in children and adolescents, in our study we considered both the global and Iraqi studies which conducted between 2014 and 2025. Genetic polymorphisms in key immune-regulating genes such as HLA, CTLA-4, INSR, IL2RA,

and PTPN22 play mechanistic roles in the development of (T1DM). HLA variants enhance antigen presentation of pancreatic  $\beta$ -cells, CTLA-4 mutations impair T-cell regulation, and IL2RA and PTPN22 polymorphisms disrupt immune tolerance, collectively contributing to  $\beta$ -cell destruction and autoimmune progression in affected children and adolescents (Lee & Hwang, 2019).

### a. HLA class II genes (HLA-DR and HLA-DQ)

A strong association with the development of autoimmune diseases, including (T1DM) (Steck & Rewers, 2011). The HLA system is one of the most powerful genetic determinants influencing (T1DM) susceptibility in children and adolescents. Notably, the HLA-DR3 and HLA-DR4 alleles are present in approximately 90% of children diagnosed with the disease, and the presence of both alleles together significantly increases genetic susceptibility (Yahaya & Salisa, 2021). The mutant allele was identified in 43% of (T1DM) patients compared to 25% of healthy controls (Yahaya & Salisa, 2021). Individuals carrying the AA or AG genotype also showed lower C-peptide levels and increased immune activation compared to those with the protective GG genotype. These findings suggest that the mutation contributes to impaired insulin-producing beta cell function and increases susceptibility to (T1DM) (Lemos et al., 2024; Steck & Rewers, 2011).

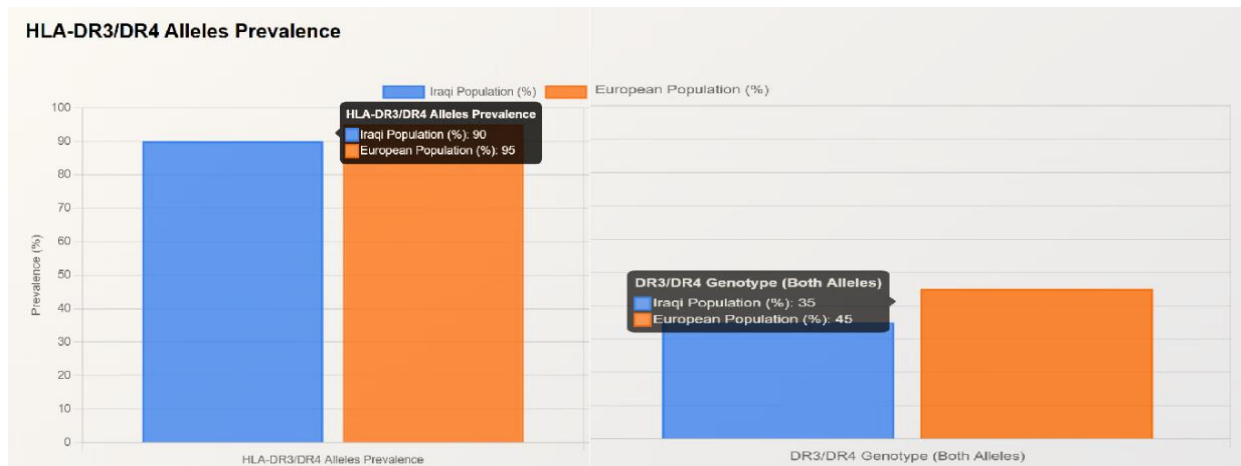
Iraqi case-control studies conducted by Zainab and Amina (2023) indicated an association between (T1DM) and HLA class II alleles in Iraqi children, particularly the DQA10503 gene, which may contribute to genetic susceptibility among children (Fayydh & Al-Thwani, 2023). A 2024 study conducted in Sulaymaniyah also reported a genetic susceptibility to (T1DM) among children carrying these genes [21]. In another case-control study conducted in Sulaymaniyah by Amin et al. (2023), a higher prevalence of autoimmune antibodies (GAD65, IAA, IA2A, and ICA) was reported among children and adolescents with (T1DM) compared to healthy controls. The researchers found that more than half of the patients were positive for ICA and IA2A antibodies, with decreased C-peptide and elevated HbA1c, confirming a strong autoimmune involvement in the disease mechanism (Hantoosh et al., 2014).

✉ Israa M. Ali Alameen: [israa.m.ali.alamee@gmail.com](mailto:israa.m.ali.alamee@gmail.com)

Tel:

Published online: 15<sup>th</sup> February, 2026

DOI: <https://dx.doi.org/10.4314/br.v23i3.1>



**Figure 1.** Comparison of the prevalence of HLA-DR3/DR4 genes and mutations in Iraqi children with (T1DM). The figure shows a higher prevalence of HLA-DR3/DR4 immunological alleles (90%) in Iraqi children compared to 95% in Europeans, with INSR mutations (rs2229429 G>A) being associated with poor glycemic control, confirming the dual role of genetic and immunological factors in disease development.

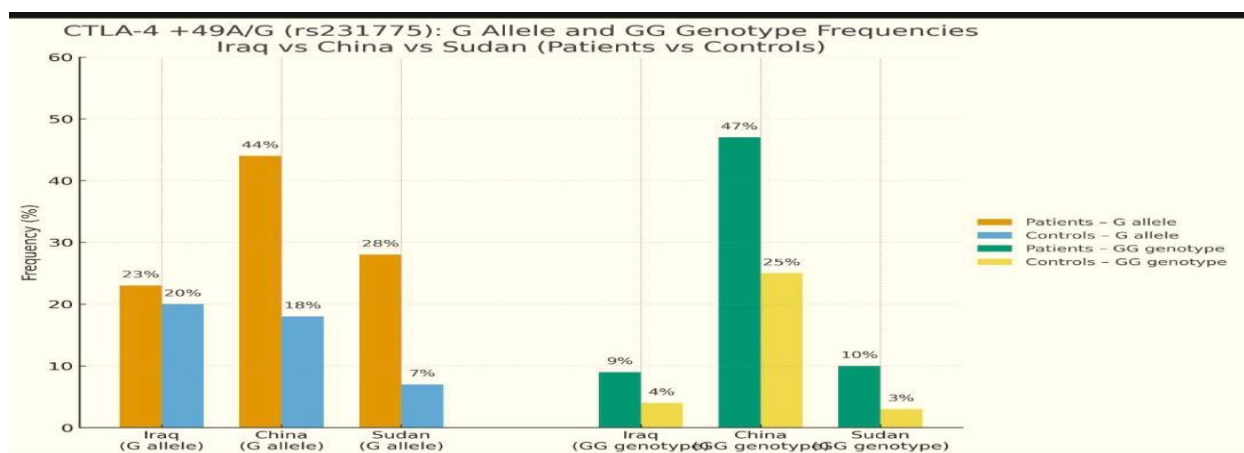
**b. INSR Gene (insulin receptor gene)**

A case-control study was conducted by AlQuraishi and Rasool (2025) to examine the impact of the INSR (rs2229429 G>A) gene polymorphism on insulin response among Iraqi children with (T1DM). The study revealed that patients carrying the AA mutant genotype were 10.47 times more likely to exhibit poor glycemic control (HbA1c > 86 mmol/mol) compared to those with the normal genotype (AlQuraishi and Rasool, 2025).

**c. CTLA4 (cytotoxic T-lymphocyte associated protein 4)**

CTLA-4 Gene (+49A/G): The CTLA-4 gene functions as a negative immune regulator that prevents the activation of T cells and inhibits the destruction of β cells in the pancreas. In (T1DM), the +49A/G polymorphism (rs231775) weakens this inhibitory mechanism, facilitating immune attacks on β cells and increasing susceptibility, especially in children. In Iraq, Al-Isawi et al. (2022) studied this relationship in 100 children (60 patients and 40 healthy) using the ARMS-PCR technique. The results

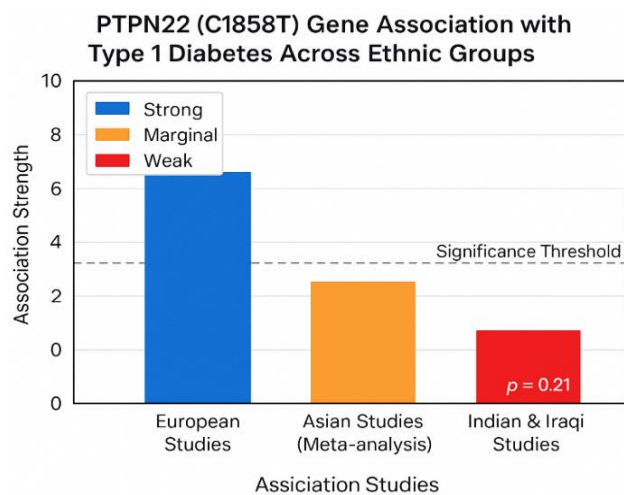
showed no significant differences in genotype distribution, although the AA genotype was more frequent among patients, indicating a genetic-immune predisposition that requires confirmation in larger studies. Comparative data from other populations support this interpretation; for instance, a study by Chen et al. (2018) in China showed that the CTLA-4 +49A/G variant is significantly associated with the risk of (T1DM) ( $p = 2.82 \times 10^{-4}$ ; OR = 1.25) and affects CTLA-4 gene expression levels in Treg cells, linking it to immune dysregulation. Similarly, a study by Kheiralla et al. (2021) in Sudan demonstrated a higher frequency of the G allele (28% vs. 7%) and the GG genotype (12% vs. 2%) among affected children compared to healthy controls ( $p < 0.01$ ), confirming the association of this polymorphism with increased autoimmune susceptibility. These results show population variation in the distribution of genotypes, but generally confirm the role of CTLA-4 +49A/G as an important immunogenetic factor in the mechanism of (T1DM) development across different populations [Al-Isawi et al., 2022; Chen et al., 2018; Kheiralla et al., 2021].



**Figure 2.** shows a comparison of the frequencies of the G allele and the GG genotype of the CTLA-4 +49A/G (rs231775) gene among children with (T1DM) in Iraq, China, and Sudan, and their corresponding healthy groups. The figure indicates that the frequencies of the G allele and GG genotype were significantly higher in Chinese and Sudanese children, suggesting a strong immunogenetic association ( $p < 0.01$  and  $p < 0.05$ , respectively), while the difference was not significant in Iraqi children.

#### d. PTPN22 (protein tyrosine phosphatase non-receptor type 22)

These results are consistent with the findings of [Anand et al. \(2019\)](#) in India, where the study did not show any significant association between the PTPN22 (C1858T) gene mutation and (T1DM) in Indian children in northern India ( $p = 0.21$ ). However, a combined meta-analysis of several Asian studies showed a marginal effect, supporting the hypothesis that susceptibility to the PTPN22 gene may vary according to ethnicity. Compared with European studies that demonstrated a strong association between this gene and the disease ([Tizaoui et al., 2021](#)), the Iraqi results appear closer to the Asian pattern, indicating a limited genetic influence and suggesting that environmental or epigenetic factors are more likely to play a larger role in disease development within the region. ([Tizaoui et al., 2021](#); [Anand et al., 2019](#)).

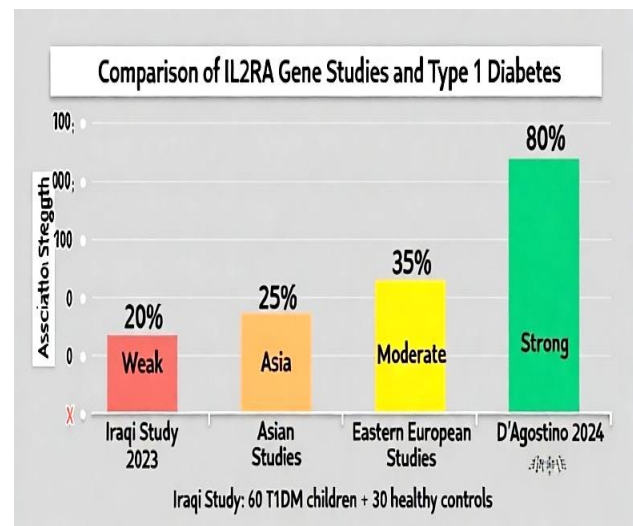


**Figure 3.** Comparison of the strength of the association between PTPN22 (C1858T) mutation and (T1DM) among European, Asian, and Iraqi/Indian populations. European studies show a strong genetic association, whereas Asian studies indicate a marginal effect, while Iraqi and Indian studies show a weak or nonsignificant association ( $p = 0.21$ ), suggesting that the genetic effect varies according to population composition.

#### e. IL2RA (interleukin-2 receptor alpha)

This Iraqi study conducted in 2023 in Dhi Qar Governorate is considered the first known attempt to investigate the relationship between the polymorphism of the IL2RA gene (rs2104286) and (T1DM) in children. The study used a case-control design, including 60 children with diabetes and 30 healthy children. Using the ARMS-PCR technique, the researchers were unable to find a significant difference in the distribution of the IL2RA gene (with the AA genotype being the most common in both groups), suggesting that there is no strong association between this genetic polymorphism and (T1DM) Although this study represents a pioneering effort, it has several limitations, such as the small sample size and the lack of correlation with clinical indicators like HbA1c or autoimmune antibodies ([D'Agostino et al., 2024](#)). When comparing the Iraqi results with studies

conducted in other populations, it appears that the findings in Iraq follow a pattern similar to several Asian and Eastern European studies, where the association between the IL2RA gene and (T1DM) was weak or absent. For example, [D'Agostino et al. \(2024\)](#) reported elevated levels of the interleukin-2 receptor and the presence of A significant relationship exists between IL2RA mutations and autoimmune diseases in children, whereas the study by [Wawrusiewicz-Kurylonek et al. \(2020\)](#) found only a marginal association between this polymorphism and autoimmune diseases. These differences suggest that ethnic background, environmental exposure, and small sample sizes may influence the variability of results across populations, supporting the need for larger multi-ethnic studies in Iraq to confirm the role of this gene in the development of (T1DM) ([D'Agostino et al., 2024](#); [Wawrusiewicz-Kurylonek et al., 2020](#)).



**Figure 4.** Comparative analysis of the association of the IL2RA gene (rs2104286) with (T1DM) across different population groups. The Iraqi study (2023) showed a weak association (20%), similar to Asian studies, while a moderate association was observed in Eastern European studies and a strong association in the study by [D'Agostino et al. \(2024\)](#).

#### f. INS (VNTR) (insulin gene with variable number tandem repeats)

Mutations in the INS gene (VNTR) play an important role in determining susceptibility to (T1DM), particularly in children. This gene regulates insulin gene expression in the thymus, enhancing immune tolerance and preventing immune cells from attacking insulin-producing beta cells. Mechanistically, changes in the VNTR sequence disrupt thymic insulin expression, impairing central immunity and allowing autoreactive T cells to escape the deletion, thus initiating beta cell destruction.

Despite its importance, no Iraqi study was conducted between 2014 and 2025 to evaluate this gene, representing a clear national research gap. Comparative studies have shown mixed results; For example, [De Nanclares et al. \(2003\)](#) demonstrated a strong association between class I

**DOI:** <https://dx.doi.org/10.4314/br.v23i3.1>

alleles and an increased risk of diabetes in Finnish children, while [Kawasaki et al. \(2011\)](#) in Japan reported a weak or non-significant association, suggesting ethnic differences in susceptibility associated with VNTR [[De Nanclares et al., 2003](#); [Wawrusiewicz-Kurylonek et al., 2020](#); [Kawasaki et al., 2011](#)]. Similarly, the IFIH1 gene plays an important role in the immune response against viruses and in the pathogenesis of (T1DM). The rs1990760 (Ala946Thr) mutation increases innate immune activity and promotes beta cell self-destruction. A recent Iraqi study (2023–2024) examined the rs1990760 and rs3747517 mutations in 60 affected and 30 healthy children, and the results showed a significant association between rs1990760 and (T1DM), while no significant effect was observed for the rs3747517 mutation. These findings are consistent with global data indicating that IFIH1 mutations increase immune hyperresponsiveness and the risk of (T1DM) ([Hassan et al., 2022](#)). Overall, the lack of studies specific to the INS VNTR gene and the limited research on IFIH1 in Iraq underscore the need for broader molecular studies to elucidate the interaction between genetic and environmental factors that cause autoimmunity in children with (T1DM) ([Jermendy et al., 2018](#)).

#### g. TYK2 (tyrosine kinase 2)

The TYK2 gene plays a regulatory role in the immune system and contributes to the destruction of pancreatic  $\beta$ -cells in individuals with (T1DM). According to animal studies, blocking this gene may protect pancreatic cells from immune attack; however, most of these findings are limited to non-human models, and no clinical trials have been conducted in humans yet. Most of the available research has been carried out on mice, and currently, there are no studies in Iraq or even across the Middle East investigating this gene. The mutation rs34536443, reported as protective in European populations, has not been tested regionally, and its effect may vary with ethnicity. Iraq urgently needs local studies to determine whether this gene plays a risk or protective role in diabetes, using modern molecular approaches to achieve more accurate results ([Chandra et al., 2022](#)). When compared with global studies, the Iraqi findings partially align with observations from other populations. For instance, [Chandra et al. \(2022\)](#) demonstrated that TYK2 directly regulates  $\beta$ -cell development and interferon- $\alpha$  signaling, confirming its mechanistic role in T1DM pathogenesis. Conversely, [Steri et al. \(2025\)](#) reported that the protective variant p.Pro1104Ala (rs34536443) reduces autoimmune susceptibility in European populations. These findings highlight ethnic and environmental variability in TYK2 activity and emphasize the need for studies based on the Iraqi population to clarify its contribution to disease onset and progression ([Chandra et al., 2022](#); [AlQuraishi & Rosool, 2025](#); [Steri et al., 2025](#)).

#### h. ERBB3 (Erb-B2 receptor tyrosine kinase 3)

The ERBB3 (Erb-B2 receptor tyrosine kinase 3) gene encodes a receptor involved in immune regulation and

intracellular signaling. The single nucleotide polymorphism rs2292239 is associated with a significantly increased risk of (T1DM) because it affects beta cell survival and modulates autoimmune responses. However, no studies have examined this gene in Iraqi or Middle Eastern samples, representing a significant research gap in regional immunogenomic studies ([AlQuraishi & Rosool, 2025](#)). Globally, several studies have confirmed this association. Sun and colleagues (2016) identified ERBB3-rs2292239 as one of the most significant non-HLA gene loci associated with (T1DM) in Chinese children, highlighting its pivotal role in immune regulation. Similarly, [Wang & Pan \(2019\)](#) conducted a meta-analysis that included data from Asian and European populations and confirmed a significant association between rs2292239 and the risk of T1DM. These findings highlight that the effect of this gene is globally established, but its expression and effect may vary across ethnicities, underscoring the need for local Iraqi studies to clarify its biological and clinical role in disease progression

#### i. CLEC16A (C-Type lectin domain family 16 member A)

The CLEC16A gene plays a vital role in pancreatic beta ( $\beta$ ) cells, controlling mitochondrial autophagy, which protects mitochondria from damage and regulates insulin secretion.

Genome-wide association studies (GWAS) in several populations—including Chinese, Japanese, and European populations—have revealed that mutations rs12708716, rs2903692, and rs725613 are significantly associated with an increased risk of (T1DM).

These mutations are believed to affect beta cell function and increase susceptibility to autoimmunity. Functional studies, such as [Soleimanpour et al. \(2014\)](#), have also shown that loss of the CLEC16A gene leads to impaired mitochondrial quality and impaired glucose regulation ([Sang et al., 2012](#)). In Iraq, no studies have yet examined CLEC16A gene mutations in children with or without diabetes, highlighting a significant local research gap in understanding the contribution of this gene to autoimmunity and beta cell protection.

Therefore, this study aims to identify and summarize the genetic and biological factors—including the CLEC16A gene—that may contribute to the development of (T1DM) in Iraqi children, and compare them with global findings to clarify the extent of regional variations. Globally, [Sang et al. \(2012\)](#), identified variants (rs2903692 and rs12708716) in the CLEC16A gene as non-HLA risk loci in Chinese children with (T1DM), suggesting that these mutations affect mitochondrial function within beta cells ([Sang et al., 2012](#)). Similarly, [Hakonarson & Barrett \(2014\)](#) provided functional evidence showing that the CLEC16A gene influences immune regulation and beta cell integrity, and that its genetic polymorphisms are significantly associated with autoimmune activity in European populations ([Hakonarson & Barrett, 2014](#)). These findings highlight the established global importance of this gene, while the lack of studies in Iraq

DOI: <https://dx.doi.org/10.4314/br.v23i3.1>

indicates an urgent need for local genetic research to confirm its biological and clinical significance.

### Autoimmunity (auto-antibodies against $\beta$ -cells)

Autoimmunity in (T1DM) occurs when the immune system loses its ability to distinguish between self and non-self-antigens, leading to the destruction of pancreatic beta cells responsible for insulin production. Several types of autoantibodies have been identified in children and adolescents with the disease, including insulin autoantibodies (IAA), GAD65 enzyme autoantibodies, and ZnT8 zinc transporter autoantibodies. According to the Human Islet Research Network (HIRN, 2024), the presence of more than one autoantibody indicates an

increased likelihood of developing the disease. International studies such as those by Ziegler et al. (2013) and Krischer et al. (2020) have confirmed that the presence of more than one type of autoantibody—particularly IAA, GAD65, and ZnT8—is a strong indicator of disease onset and progression in genetically predisposed children (Herold et al., 2013). These results highlight the importance of conducting similar immunological studies in Iraq, where research in this field is still limited. However, there are no Iraqi studies that have addressed this important immunological aspect, which limits the understanding of the immune profile of local patients. Therefore, this review aims to shed light on this research gap and provide updated comparative evidence to guide future research efforts in Iraq.

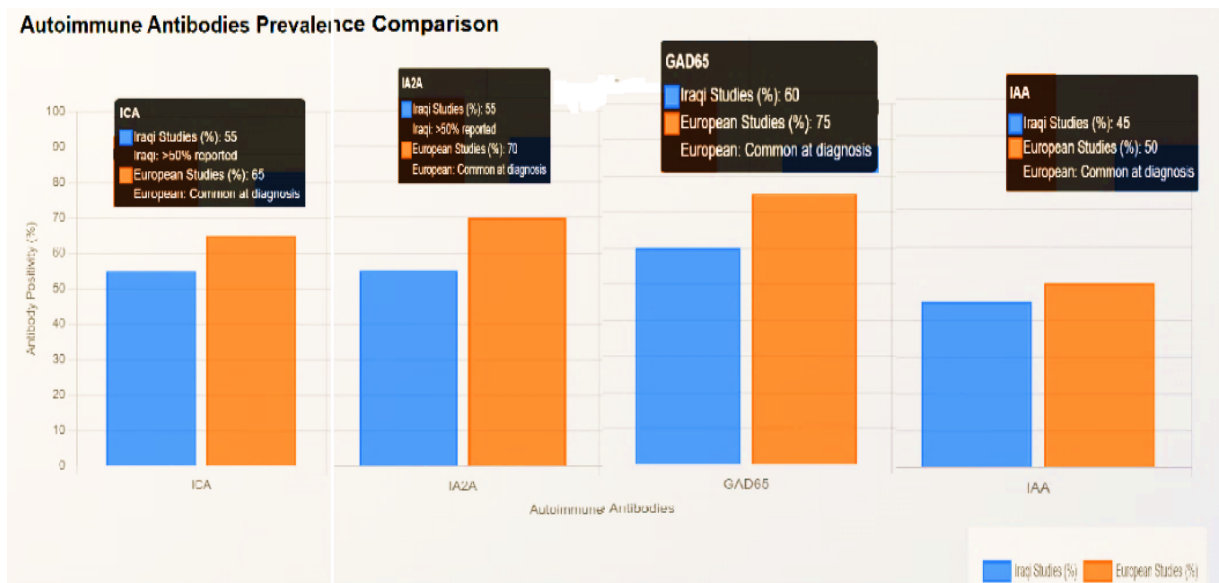
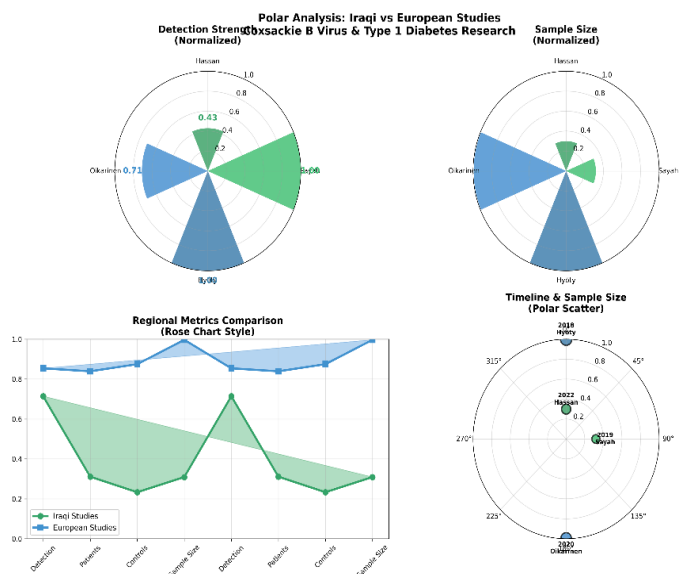


Figure 5. Comparison of the prevalence of autoantibodies between Iraqi and European studies in children with (T1DM). The figure illustrates the prevalence rates of the main autoantibodies (ICA, IA2A, GAD65, and IAA) among Iraqi children with (T1DM) compared to European cohorts. Iraqi studies showed slightly lower rates (45–60%) compared to European studies (50–75%), suggesting the possibility of differences in the intensity of immune system activation or the timing of diagnosis.

### Viral Triggers (Coxsackie B Virus)

Two studies conducted in Iraq have provided evidence that viruses, particularly Coxsackie B virus, may act as environmental triggers for the development of (T1DM). In 2022, Hassan et al., examined 75 children with (T1DM) and 75 healthy children and found that 13.3% of patients had Coxsackie B IgG antibodies, with a strong association with antibodies to insulin-producing cells (GAD65, IA-2A, and ICA), suggesting an autoimmune mechanism induced by the virus (Hassan et al., 2022). Similarly, Sayah & Mezher (2019) conducted a study that included detection of active or previous Coxsackie B4 infection in 31% of children with diabetes using PCR. Genetic analyses showed that the detected viral strain was highly similar to the global B4 strain (Krischer et al., 2020). Similar findings have been reported by global studies, such as Hyöty et al. (2018) in Finland & Oikarinen et al. (2020) in Sweden, which confirmed that Coxsackie B infection is significantly associated with beta-cell autoimmunity



DOI: <https://dx.doi.org/10.4314/br.v23i3.1>

and the development of (T1DM), especially in children with a genetic predisposition to the disease (Sayah & Mezher, 2019).

## Discussion

The current findings demonstrate that (T1DM) in Iraqi children results from a complex interplay of genetic, immunological, and viral factors. Comparison with global studies reveals that some genes share similar patterns to those observed in Asian populations, while others exhibit marked differences from Europeans, as shown in Figures 1–6.

As shown in Figure 1, we note that the HLA-DR3 and HLA-DR4 alleles are among the strongest genetic determinants of disease susceptibility, reaching approximately 90% among Iraqi children, close to what has been reported in European studies (Yahaya & Salisa, 2021). However, the frequency of the DR3/DR4 genotype was lower (35% in Iraq versus 45% in Europe), suggesting a relatively less severe genetic susceptibility in the local population.

Figure (2) shows that the CTLA-4 (+49A/G) variant did not show a significant difference between patients and healthy controls in Iraq. This is consistent with Al-Isawi et al., (2018), but differs from the results of Chen et al. (2018) in China and Kheiralla et al. (2021) in Sudan, where the G allele was associated with an increased risk of infection. This discrepancy is attributed to differences in ethnic background and environmental factors that influence the regulation of autoimmunity. As shown in the Figure 3, the PTPN22 (C1858T) mutation shows a weak association with disease in Iraq, which is consistent with what Anand et al. (2019) reported in India, while European studies such as Tizaoui et al. (2021), showed a strong association with autoimmunity. This observation suggests that the effect of this gene depends on the regional genotype and accompanying environmental factors. In addition,  $\beta$ -cell destruction in (T1DM) is linked to a complex immunological cascade, as illustrated in Figure 1. Antigen-presenting cells present  $\beta$ -cell peptides through HLA class II molecules, subsequently activating autoreactive CD4<sup>+</sup> T helper cells. These cells, in turn, stimulate cytotoxic CD8<sup>+</sup> T cells and secrete pro-inflammatory cytokines such as IL-1 $\beta$ , IFN- $\gamma$ , and TNF- $\alpha$ , which accelerate  $\beta$ -cell apoptosis and amplify autoimmune inflammation. The interaction between genetic susceptibility (particularly HLA-DR3/DR4 and CTLA-4 variants) and immune dysfunction is the basis for  $\beta$ -cell destruction in genetically predisposed individuals. Furthermore, IL2RA gene polymorphisms may reduce T-cell regulatory control, enhancing immune activation and perpetuating chronic inflammation. Together, these findings highlight the interplay between genetic and immunological mechanisms underlying (T1DM) in Iraqi children. In Figure 4, we note that the IL2RA variant (rs2104286) shows a weak association in Iraq compared to European studies like D'Agostino et al., (2024). This is consistent with the findings of Wawrusiewicz-Kurylonek

et al. (2020) in Poland, confirming that the genetic immune response varies according to ethnic origin. As shown in Figure 5, it is clear that the CLEC16A gene plays a key role in maintaining mitochondrial integrity and regulating insulin secretion. Global studies (Hakonarson et al., 2014 and Soleimanpour et al., 2014) have shown that its variants are associated with an increased risk of infection. However, no Iraqi or Middle Eastern studies have been conducted on this gene, creating a clear research gap. The same applies to TYK2 and ERBB3, which studies (Steri et al., 2025; Nejentsev et al., 2009) have shown to regulate autoimmunity. However, the lack of Iraqi data on these autoantibodies limits a full understanding of the disease-causing mechanisms. From an immunological perspective, the data in Figure 6, show that the autoantibodies ICA, IA-2A, GAD65, and IAA were positive in 45–60% of Iraqi children, slightly lower than those reported in Europe (50–75%) [22, 23]. This lower rate may be attributed to delayed diagnosis or a lack of laboratory testing, but the presence of more than one autoantibody, particularly GAD65 and ZnT8, remains a clear indicator of advanced autoimmune disease. Regarding environmental factors, Iraqi studies have revealed that Coxsackie B virus was found in 13–31% of patients, a lower percentage than documented in Scandinavian studies (40–50%) Krischer et al., 2020; Hassan et al., 2022; Saya & Mezher, 2019). This supports the view that viral infection represents an environmental trigger that increases autoimmune activity in genetically susceptible children. Comparing Iraqi findings with international ones, a recurring pattern emerges: genes (such as CTLA-4, PTPN22, and IL2RA) are weaker or inconsistently associated with diabetes compared to Europeans and more closely related to Asia and parts of Africa. This suggests population genetic peculiarities and context-dependent immune activation. Repeated viral exposures, dietary restrictions, and environmental stress may modulate cytokine signaling and T-cell regulation, reducing the permeability of genetic risk and shifting pathological expression toward an immune-environment interaction. This is supported by the Iraqi CTLA-4 and IL2RA findings compared to China/Sudan/India and the heterogeneity of PTPN22 signaling across regions. In conclusion, the Iraqi pattern is explained by an integrative model in which modest genetic susceptibility interacts with immune dysfunction and viral triggers, necessitating multicenter studies that measure genetic, viral, and immune markers together. In summary, the results across Figures 1–6 show that Iraqi children share basic disease pathways with Asian populations, but the genetic and immunological associations are weaker than those reported in Europe. This highlights the need for multicenter, national studies that combine genetic, immunological, and viral analysis to gain a deeper understanding of (T1DM) in Iraq. In addition to genetic

**DOI:** <https://dx.doi.org/10.4314/br.v23i3.1>

and immunological factors, clinical management of (T1DM) in Iraq remains a major challenge. Limited access to advanced insulin analogs, continuous glucose monitoring devices, and specialized pediatric diabetes centers has contributed to poor glycemic control in many patients. Moreover, economic barriers and low public awareness hinder early diagnosis and adherence to treatment. Addressing these limitations requires national strategies aimed at improving pediatric endocrinology services, ensuring a consistent insulin supply, and implementing structured educational programs for patients and their families (Scaccia, 2025).

Iraqi studies investigating genetic, immunological, and viral factors in (T1DM) share several methodological limitations, most notably small sample sizes, poor methodological design, and the absence of multicenter or long-term studies. Genetic research has often focused on simple association analyses without delving into molecular mechanisms. Important genes such as TYK2, ERBB3, CLEC16A, and IFIH1 have not been investigated in Iraq or the surrounding region. Immunological studies have relied on outdated serological tests for detecting autoantibodies (IAA, GAD65, ZnT8) without molecular confirmation or long-term follow-up. Virological studies, particularly those related to Coxsackie B virus, have been limited in terms of sample numbers, timing of testing, and the lack of genetic analysis of the virus. These methodological limitations reduce the accuracy and general applicability of the results, highlighting the urgent need for large-scale, systematic studies at the molecular and population levels in Iraq. Addressing these limitations will enhance the reliability of future research in this area.

## Conclusion

Although immune-related genes such as HLA and CTLA-4 play a key role in (T1DM), there is a clear lack of research in this area in Iraq. Most available studies used outdated methods and relied on small samples, limiting the accuracy and generalizability of the findings. Moreover, several important genes—such as TYK2, PTPN22, IL2RA, ERBB3, CLEC16A, and IFIH1—have not been systematically investigated in Iraq, despite their globally recognized role in immune regulation and pancreatic beta cell function. Autoimmune antibodies and viral triggers

such as Coxsackievirus B have also not been adequately explored, despite global evidence suggesting their importance in disease initiation.

Therefore, there is an urgent need for new, large-scale studies based on modern, population-based methodologies to better elucidate the biological mechanisms, improve early detection, and enhance prevention strategies, particularly among children and adolescents in Iraq. These findings may contribute to guiding future efforts toward developing effective diagnostic and preventive tools for (T1DM) in Iraq.

## Recommendation

It is strongly recommended to initiate large-scale, multicenter studies that include genetic and immunological analyses, employing advanced molecular techniques such as next-generation sequencing (NGS), gene expression profiling, and longitudinal immunological monitoring to understand the complex genetic and environmental factors that lead to (T1DM) in Iraqi children and adolescents.

These studies should aim to establish a national genetic and immunological database, improve early detection tools, and develop targeted preventive programs for high-risk groups of children.

## List of Abbreviations

### Declaration

### Acknowledgment

The authors would like to acknowledge all researchers whose studies and findings have contributed to the development of this review.

### Funding

This research received no external funding.

### Data Availability Statement

This study is based on publicly available data from published research sources, and all data used are cited in the references list.

### Conflicts of Interest

The authors declare no conflict of interest.

### Ethical Approval

Not Applicable

## References

- Al Ashoor, M., Al Hamza, A., Zaboob, I., Almomin, A., & Mansour, A (2022). Prevalence and risk factors of diabetic retinopathy. *Iraq. J Med Life*, 2(2):299-306. doi: 10.25122/jml-2022-0170.
- Al-Isawi, H. R., Safi, F., & Muhammed, H. A. (2022). Association of CTLA-4 (+49A/G) gene polymorphism with type 1 diabetes mellitus in Iraqi children. *Cellular and Molecular Biology*, 68(5), 1–6. <https://doi.org/10.14715/cmb/2022.68.5.1>
- Al-Quraishi, F. A., & Rasool, M. I. (2025). Impact of INSR (rs2229429) G>A genetic polymorphism on response to exogenous insulin in type 1 diabetic Iraqi patients. *Wiadomości Lekarskie*, 78(1):71–81. <https://doi.org/10.36740/WLek/199949>
- AlQuraishi, F. A., & Rasool, M. I. (2025). Impact of INSR (rs2229429) G>A genetic polymorphism on response to exogenous insulin in type 1 diabetic Iraqi patients. *Wiadomości Lekarskie*, 1:71–81. <https://doi.org/10.36740/wlek/199949>
- Alsharairi, N. A. (2024). Diagnostic biomarkers of microvascular complications in children and adolescents with type 1 diabetes mellitus; An updated review. *Pediatric Reports*, 16(3):763–778. <https://doi.org/10.3390/pediatric16030064>
- Anand, A., Singh, S., Kumar, S., & Nandini, S. (2019). Association of PTPN22 gene polymorphism

DOI: <https://dx.doi.org/10.4314/br.v23i3.1>

- (C1858T) with Type 1 Diabetes Mellitus in North Indian children: A case-control study and meta-analysis. *Human Immunology*, 80(6):433–439. <https://doi.org/10.1016/j.humimm.2019.02.011>
- Antar, S. A., Ashour, N. A., Sharaky, M., Khattab, M., Ashour, N. A., Zaid, R. T., Roh, E. J., Elkamhawy, A., & Al-Karmalawy, A. A. (2023). Diabetes mellitus: classification, mediators, and complications; A gate to identify potential targets for the development of new effective treatments. *Biomedicine & Pharmacotherapy*, 168: 115734. <https://doi.org/10.1016/j.biopha.2023.115734>
- Chandra, V., Ibrahim, H., Halliez, C., Prasad, R. B., Vecchio, F., Dwivedi, O. P., et al. (2022). The type 1 diabetes gene TYK2 regulates  $\beta$ -cell development and its responses to interferon- $\alpha$ . *Nature Communications*, 13(1). <https://doi.org/10.1038/s41467-022-34069-z>
- Chandra, V., Ibrahim, H., Halliez, C., Prasad, R. B., Vecchio, F., Dwivedi, O. P., et al. (2022). The type 1 diabetes gene TYK2 regulates  $\beta$ -cell development and its responses to interferon- $\alpha$ . *Nature Communications*, 13(1), 6782. <https://doi.org/10.1038/s41467-022-34069-z>
- Chen, Y., Chen, S., Gu, Y., Feng, Y., Shi, Y., Fu, Q., Wang, Z., Cai, Y., Dai, H., Zheng, S., Sun, M., Zhang, M., Xu, X., Chen, H., Xu, K., & Yang, T. (2018). CTLA-4 +49 G/A, a functional T1D risk SNP, affects CTLA-4 level in Treg subsets and IA-2A positivity, but not beta-cell function. *Scientific Reports*, 8(1), 10074. <https://doi.org/10.1038/s41598-018-28423-9>
- D'Agostino, S., Valentini, G., & Dolci, M. (2024). Exploring interleukin levels in type 1 diabetes and periodontitis: A review with a focus on childhood. *Children (Basel)*, 11(2):238. <https://doi.org/10.3390/children11020238>
- De Nancrales, G. P., Bilbao, J. R., Calvo, B., Vitoria, J. C., Vázquez, F., & Castaño, L. (2003). 5'-Insulin gene VNTR polymorphism is specific for type 1 diabetes. *Annals of the New York Academy of Sciences*, 1005(1):319–323. <https://doi.org/10.1196/annals.1288.050>
- Fayyadh, Z., & Al-Thwani, A. N. (2023). Molecular and demographic study about type 1 diabetes mellitus and associated with HLA typing class II in a sample of Iraqi children. *University of Baghdad*. <https://www.researchgate.net/publication/376722941>
- Hakonarson, H., & Barrett, J. C. (2014). Fine mapping and functional studies of risk variants for type 1 diabetes. *Diabetes*, 63(12):4360–4368. <https://doi.org/10.2337/db14-0333>
- Hammoud, M. S., Alawsi, F. A. F., Ali, S. H., & Baban, R. S. (2023). Risk factors of diabetic nephropathy among a group of Iraqi children with type 1 diabetes mellitus. *Iraqi Journal of Medical Sciences*, 21(1):48–55. <https://doi.org/10.22578/IJMS>
- Hantoosh, M. H., Al-Hilaly, H. A., & Jabir, F. A. (2014). Frequencies of HLA-DR3 and DR4-among-type-1-diabetes-mellitus. *College of Medicine, University of Al-Qadisiyah*. <https://repository.qu.edu.iq/wp-content/uploads/sites/31/2016/11/>
- Hassan, F. H., Al-Saadi, M. A., & Al-Abudi, A. N. (2022). Association of anti-coxsackievirus-B IgG with autoantibodies related to type 1 diabetes mellitus. *Iraqi Journal of Medical Sciences*, 20(2), 165–174. <https://doi.org/10.22578/IJMS.20.2.6>
- Hassan, H. G., Al-Shuwaikh, A. M., & Al-Auqili, R. K. (2022). Evaluation of possible association of interferon-induced helicase (IFIH1) gene polymorphism with type 1 diabetes mellitus in a sample of Iraqi children. *Human Gene*, 33:201064. <https://doi.org/10.1016/j.humgen.2022.201064>
- Herold, K. C., Delong, T., Perdigoto, A. L., Biru, N., Brusko, T. M., & Walker, L. S. K. (2024). The immunology of type 1 diabetes. *Nature Reviews Immunology*, 24(6), 435–451. <https://doi.org/10.1038/s41577-023-00985-4>
- Hossain, M. J., Al-Mamun, M., & Islam, M. R. (2024). Diabetes mellitus, the fastest growing global public health concern: Early detection should be focused. *Health science reports*, 7(3):e2004. <https://doi.org/10.1002/hsr2.2004>
- Hossain, M. J., Al-Mamun, M., & Islam, M. R. (2024). Diabetes mellitus, the fastest growing global public health concern: Early detection should be focused. *Health Science Reports*, 7(3), e2004. <https://doi.org/10.1002/hsr2.2004>
- International Diabetes Federation. (2025). Undiagnosed Diabetes: Global Proportion (20–79 y) | IDF Atlas. <https://diabetesatlas.org/data-by-indicator/diabetes-estimates-20-79-y/proportion-of-people-with-undiagnosed-diabetes>.
- Jermendy, Á., Szatmári, I., Körner, A., Szabó, A. J., Tóth-Heyn, P., & Hermann, R. (2018). Association between interferon-induced helicase (IFIH1) rs1990760 polymorphism and seasonal variation in the onset of type 1 diabetes mellitus. *Pediatric Diabetes*, 19(2):300–304. <https://doi.org/10.1111/pedi.12569>
- Kawasaki, E., Imagawa, A., & Yamada, K. (2011). Genetic susceptibility to type 1 diabetes in Asian populations. *Annals of the New York Academy of Sciences*, 1281(1):17–32. <https://doi.org/10.1111/j.1749-6632.2011.06333.x>
- Kheiralla, K. E. K. (2021). CTLA-4 (+49A/G) polymorphism in type 1 diabetes children of Sudanese population. *Journal of Laboratory Physicians*, 13(2), 154–160. <https://doi.org/10.1055/s-0041-1725046>
- Krischer, J. P., et al. (2020) The 6-year incidence of diabetes-associated autoantibodies in genetically at-risk children: The TEDDY study. *Diabetologia*, 63(7), 1337–1348. <https://doi.org/10.1007/s00125-020-05116-8>
- Kumar, M., Yip, L., Wang, F., Marty, S. E., & Fathman, C. G. (2025). Autoimmune disease: genetic susceptibility, environmental triggers, and immune dysregulation. Where can we develop therapies?.

DOI: <https://dx.doi.org/10.4314/br.v23i3.1>

- Frontiers in immunology, 16, 1626082. <https://doi.org/10.3389/fimmu.2025.1626082>
- Lee, H. S., & Hwang, J. S. (2019). Genetic aspects of type 1 diabetes. *Annals of pediatric endocrinology & metabolism*, 24(3), 143–148. <https://doi.org/10.6065/apem.2019.24.3.143>
- Lee, J. J. I., Zampetti, S., Pozzilli, P., & Buzzetti, R. (2024). Type 2 diabetes in children and adolescents: Challenges for treatment and potential solutions. *Diabetes Research and Clinical Practice*, 217:111879. <https://doi.org/10.1016/j.diabres.2024.111879>
- Lemos, J. R. N., Hirani, K., & von Herrath, M. (2024). Immunological and virological triggers of type 1 diabetes: Insights and implications. *Frontiers in Immunology*, 14, 1326711. <https://doi.org/10.3389/fimmu.2023.1326711>
- Lucier, J., & Mathias, P. M. (2024). Type 1 diabetes. In StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK507713/>
- Magliano, D. J., Boyko, E. J., & International Diabetes Atlas Committee. (2021). Global picture. In IDF Diabetes Atlas. Brussels: *International Diabetes Federation*. <https://www.ncbi.nlm.nih.gov/books/NBK581940/>
- Ogle, G. D., James, S., Dabelea, D., Pihoker, C., Svensson, J., Maniam, J., et al. (2021). Global estimates of incidence of type 1 diabetes in children and adolescents. *Diabetes Research and Clinical Practice*, 183, 109083. <https://doi.org/10.1016/j.diabres.2021.109083>
- Ries, J. (2023). *What actually causes type 1 diabetes?* SELF. <https://www.self.com/story/type-1-diabetes-causes>
- Sang, Y., Zong, W., Yan, J., & Liu, M. (2012). The correlation between the CLEC16A gene and genetic susceptibility to type 1 diabetes in Chinese children. *International Journal of Endocrinology*, 245384. <https://doi.org/10.1155/2012/245384>
- Sang, Y., Zong, W., Yan, J., & Liu, M. (2012). The correlation between the CLEC16A gene and genetic susceptibility to type 1 diabetes in Chinese children. *International Journal of Endocrinology*, 245384. <https://doi.org/10.1155/2012/245384>
- Sawyer, B., Hilliard, E., Hackney, K. J., & Stastny, S. (2022). Barriers and strategies for type 1 diabetes management among emerging adults: A qualitative study. *Clinical Medicine Insights: Endocrinology and Diabetes*, 15:11795514221098389. <https://doi.org/10.1177/11795514221098389>
- Sayah, T. H., & Mezher, A. M. (2019). Assessment of coxsackie virus B4 in type 1 diabetes mellitus patients in Iraq. *Research Journal of Pharmacy and Technology*, 12(2), 853–857. <https://doi.org/10.5958/0974-360X.2019.00145.1>
- Scaccia, J. (2025). A silent crisis in Iraq's public health – This week in public health. *This Week in Public Health*. <https://thisweekinpublichealth.com/blog/2025/03/04/a-silent-crisis-in-iraqs-public-health>
- Scaccia, J. (2025). A silent crisis in Iraq's public health, this week in public health. *This Week Public Health*. <https://thisweekinpublichealth.com/blog/2025/03/04/a-silent-crisis-in-iraqs-public-health/>
- Steck, A. K., & Rewers, M. J. (2011). Genetics of type 1 diabetes. *Clinical Chemistry*, 57(2), 176–185. <https://doi.org/10.1373/clinchem.2010.148221>
- Steri, M., Melis, C., & Cucca, F. (2025). TYK2 p.Pro1104Ala variant protects against autoimmunity, including type 1 diabetes. *Immunology*, 176(3), 425–439. <https://doi.org/10.1111/imm.13902>
- Sun, C., Hu, Z., Lu, L., et al. (2016). ERBB3-rs2292239 as the primary type 1 diabetes association locus among non-HLA genes in Chinese Han population. *Scientific Reports*, 6:23128. <https://doi.org/10.1038/srep23128>
- Thomas, R., & Ng, S. (2020). Risks and prevalence of diabetic retinopathy in children and young people with type 1 diabetes mellitus. *Journal of Diabetes Clinical Research*, 2(3). <https://doi.org/10.33696/diabetes.1.021>
- Tizaoui, K., Terrazzino, S., Cargnin, S., Lee, K. H., Gauckler, P., & Li, H. (2021). The role of PTPN22 in the pathogenesis of autoimmune diseases: A comprehensive review. *Seminars in Arthritis and Rheumatism*, 51(3):513–522. <https://doi.org/10.1016/j.semarthrit.2021.03.004>
- Wang, D., & Pan, G. (2019). The association between rs2292239 polymorphism in ERBB3 gene and type 1 diabetes: A meta-analysis. *BioMed Research International*, 7689642. <https://doi.org/10.1155/2019/7689642>
- Wawrusiewicz-Kurylonek, N., Gościak, J., Chorąży, M., Siewko, K., Posmyk, R., & Zajkowska, A. (2020). The interferon-induced helicase C domain-containing protein 1 gene variant (rs1990760) as an autoimmune-based pathology susceptibility factor. *Immunobiology*, 225(1):151864. <https://doi.org/10.1016/j.imbio.2019.10.013>
- Yahaya, T., & Salisu, T. (2021). Genes predisposing to type 1 diabetes mellitus and pathophysiology: A narrative review. *arXiv*. <https://arxiv.org/abs/2101.06680>
- Ziegler, A. G., et al. (2013) Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *JAMA*, 309(23):2473–2479. <https://doi.org/10.1001/jama.2013.6285>

**Publisher's Note:** Bio-Research remains neutral with regard to jurisdictional claims in published maps and institutional affiliations. Bio-Research or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.