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Integration of PTP1B Genetic Variation and Clinical Factors in Risk Stratification of Insulin Resistance in Type 2 Diabetes Mellitus; Scoping Review

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Abstract
Background: Type 2 diabetes mellitus (T2DM) is a complex metabolic disease characterized by insulin resistance. The protein Tyrosine Phosphatase 1B (PTP1B) acts as a negative regulator of insulin signaling pathways, and its genetic variation is known to affect insulin sensitivity. The integration of PTP1B genomic data with clinical factors such as BMI, age, and metabolic parameters has the potential to improve the accuracy of insulin resistance risk stratification. Objective: This study aims to review the potential integration of PTP1B genetic variation with clinical factors in the risk stratification of insulin resistance in patients with T2DM. Methods: This study uses a scoping review method by searching the literature through PubMed, Scopus, and Google Scholar (2016–2025) using related keywords. Relevant articles were selected based on inclusion-exclusion criteria and analyzed qualitatively through narrative synthesis. Results: PTP1B variations such as rs6067472, rs2143511, and rs3787348 showed associations with insulin resistance, adiposity, and metabolic response. These genetic effects are influenced by clinical factors, especially BMI and physical activity, and are amplified by epigenetic mechanisms in the form of promoter methylation, which overall improves risk stratification ability. Conclusions: The integration of PTP1B genetic variation with clinical and epigenetic factors provides a comprehensive approach in stratification of insulin resistance risk in T2DM, and has the potential to support the implementation of more accurate and personalized precision medicine..

Keyword: Clinical Factors; Gene; PTP1B 1; T2DM; And Variation.

1. Introduction

The global prevalence of Type 2 Diabetes Mellitus (T2DM) has increased markedly, from approximately 200 million cases in 1990 to nearly 830 million in 2022, and is projected to reach 1.27 billion by 2050. In Indonesia, the International Diabetes Federation (2025) reported approximately 20.4 million cases, with obesity recognized as a major risk factor. Molecularly, this condition is related to the disruption of the insulin signaling pathway that normally regulates glucose homeostasis through activation of insulin receptors, IRS, and PI3K/Akt cascade to GLUT4 translocation. Protein Tyrosine Phosphatase 1B (PTP1B) acts as a negative regulator by dephosphorylating insulin receptors and IRS; overactivation of this protein inhibits the transduction of insulin signals, decreases the PI3K/Akt the activation, as well as reduces GLUT4 translocation, thereby contributing to insulin resistance and T2DM pathogenesis (Akhundova et al., 2023; Jia et al., 2024; Duarte et al., 2025; Q. Huang et al., 2017).

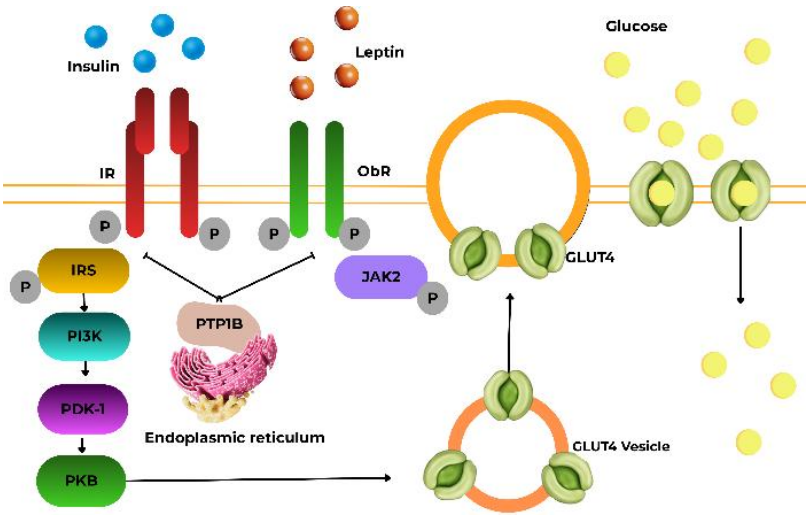


Figure 1. Insulin And Leptin Signaling Pathway.

Genetic variations in PTPN1 are associated with altered insulin responses through single-nucleotide polymorphisms that affect PTP1B activity and disrupt glucose homeostasis. This confirms the role of PTP1B as a biomarker candidate in risk stratification and therapeutic development in T2DM. Apart from genetic predisposition, insulin resistance is affected by several clinical determinants, including body mass index, sex, and age, which contribute to the characterization of metabolic phenotypes. An integrative approach that combines genomic and clinical data is considered superior to a single analysis, as it can improve the accuracy of risk prediction and support the application of precision medicine in the identification of high-risk individuals and optimization of therapeutic interventions (Fakhruzain & Tuba, 2024; Tsou & Bence, 2012; Brown & Walker, 2016; Danesh Doost et al., 2025; Piko et al., 2020).

Physiologically, the binding of insulin to the extracellular subunit of the insulin receptor (IR) triggers the autophosphorylation of tyrosine residues within the intracellular kinase domain. This process activates the receptor to recruit and phosphorylate insulin receptor substrate (IRS) proteins, specifically IRS-1 and IRS-2. Tyrosine phosphorylation of IRS subsequently acts as a docking site for phosphoinositide 3-kinase (PI3K), which in turn activates protein kinase B (Akt). Activated Akt regulates various metabolic effects of insulin, including the translocation of glucose transporter 4 (GLUT4) from intracellular compartments to the plasma membrane to facilitate glucose uptake by skeletal muscle and adipose tissue.

Protein Tyrosine Phosphatase 1B (PTP1B), encoded by the *PTPN1* gene, is localized on the cytosolic surface of the endoplasmic reticulum and acts as a primary negative regulator in this cascade. PTP1B specifically hydrolyzes phosphate groups from phosphotyrosine residues on IR and IRS-1, thereby returning these proteins to their inactive states. Through this signal termination, PTP1B prevents overactivation of the PI3K/Akt pathway. However, under pathological conditions such as obesity and chronic inflammation, the expression and catalytic activity of PTP1B are significantly upregulated in insulin target tissues, leading to premature termination of insulin signaling.

Hyperactivity of PTP1B directly disrupts the interaction between IRS-1 and PI3K, resulting in the downregulation of downstream Akt signaling. Without adequate Akt phosphorylation, the signal to mobilize GLUT4-containing vesicles to the cell surface becomes severely weakened. Consequently, peripheral cells fail to absorb glucose from the bloodstream despite elevated plasma insulin levels. This inhibition of GLUT4 translocation constitutes the molecular foundation of cellular insulin resistance, which gradually drives pancreatic beta-cell dysfunction and the clinical manifestation of T2DM.

In addition to controlling insulin signaling, PTP1B plays a central role in regulating leptin signaling within the hypothalamus. Leptin is an adipose-derived hormone responsible for controlling appetite and energy expenditure by binding to the leptin receptor (Ob-R), which activates the Janus kinase 2 (JAK2) and signal transducer and activator of transcription 3 (STAT3) pathway. PTP1B acts as a negative regulator of this pathway by docking onto and dephosphorylating JAK2, thereby limiting STAT3 activation and suppressing anorexigenic (appetite-suppressing) signals.

In obese states, excessive leptin production (hyperleptinemia) occurs alongside increased fatty tissue mass. Chronic exposure to high leptin levels triggers an upregulation of PTP1B expression as a biological feedback mechanism. Unfortunately, this hypothalamic upregulation of PTP1B induces leptin resistance, wherein the brain fails to respond to satiety signals. The resulting blockade of the JAK2/STAT3 pathway leads to persistent hunger and decreased basal energy expenditure, creating a vicious cycle that exacerbates adiposity accumulation.

The impact of obesity-induced PTP1B elevation is not limited to the hypothalamus but extends to peripheral metabolic tissues. Hypertrophied adipose tissue releases pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6). These cytokines stimulate cellular stress pathways that further increase the transcription of the *PTPN1* gene. Consequently, the obese phenotype not only worsens central leptin resistance but also accelerates peripheral insulin resistance through molecular convergence pathways mediated by PTP1B.

The *PTPN1* gene, located on chromosome 20q13.1-q13.2, has long been identified as a major susceptibility locus for obesity and T2DM. Multiple Genome-Wide Association Studies (GWAS) have demonstrated that single-nucleotide polymorphisms (SNPs) within this gene can alter protein expression levels or mRNA stability of PTP1B. These genetic variations differ significantly across ethnic populations, offering distinct contributions to individual metabolic risks.

One of the most widely studied categories of SNPs involves variations in non-coding regions, including promoter and untranslated regions (UTRs). Polymorphisms in these areas often affect transcription factor binding sites or mRNA translation efficiency, leading to constitutive overexpression of PTP1B. Individuals carrying specific risk alleles exhibit a pronounced decline in insulin sensitivity, characterized by elevated Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) indices even prior to the clinical onset of diabetes.

Furthermore, genetic variations within exonic regions possess the potential to alter the tertiary structure of the PTP1B enzyme, increasing its binding affinity to the insulin receptor or rendering it resistant to normal proteasomal degradation. The accumulation of *PTPN1* risk variants within a genome creates a genetic burden that

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consistently suppresses metabolic plasticity. Therefore, identifying *PTPN1* SNP profiles offers an excellent opportunity as a genomic biomarker for the early detection of individuals prone to insulin signaling failure.

Although the genetic architecture lays the foundation for metabolic susceptibility, the overt manifestation of insulin resistance is profoundly influenced by conventional clinical determinants. Aging is inherently associated with a decline in skeletal muscle mass (sarcopenia) and an increase in visceral fat deposition. Molecularly, the aging process is accompanied by elevated cellular oxidative stress and mitochondrial dysfunction, which cooperate with PTP1B activity to exacerbate the degradation of insulin receptor substrates.

The biological sex factor also mediates this risk through the influence of sex steroid hormones on adipose distribution and insulin sensitivity. Estrogen is known to exert protective effects by suppressing PTP1B expression in adipose tissue and enhancing GLUT4 functionality. Conversely, the post-menopausal decline in estrogen triggers a redistribution of fat from subcutaneous to visceral depots, accompanied by a spike in PTP1B expression, explaining why T2DM risk rises sharply in women after entering menopause.

Body Mass Index (BMI) and other adiposity parameters act as primary clinical catalysts that amplify the genetic effects of *PTPN1*. An elevated BMI reflects an expansion of adipose tissue, which serves as a major source of free fatty acids (FFAs) and inflammatory cytokines. High circulating FFAs activate stress kinases such as JNK and PKC, which act synergistically with PTP1B to block the insulin pathway. Thus, a patient's current clinical status reflects the macroenvironment in which *PTPN1* genetic variants express their pathological influence.

To date, risk stratification for T2DM in clinical practice remains largely reliant on conventional parameters such as fasting blood glucose, HbA1c, and BMI assessments. While these methods are highly effective for diagnosis, their capacity to predict the rate of disease progression or individual therapeutic response is limited. Two individuals with identical BMI and HbA1c levels often exhibit entirely different clinical trajectories—a variability largely driven by their genetic background.

Integrating genomic data, particularly *PTPN1* gene variations, with longitudinal clinical data (such as age, sex, lipid profiles, and family history) offers a comprehensive solution through multi-dimensional risk modeling. A Polygenic Risk Score (PRS) that combines PTP1B genetic variants with clinical phenotypic factors can quantify an individual's absolute probability of experiencing worsening insulin resistance. Through this mathematical approach, the shortcomings of single-modality analysis—where pure genetic data ignores environmental factors, and pure clinical data ignores hereditary predisposition—can be overcome.

This integrative model enables the creation of a data architecture capable of capturing complex gene-environment interactions. For instance, the pathological effect of a specific *PTPN1* risk allele might only be fully activated if the patient's BMI exceeds a certain threshold or if they belong to an older age group. By mapping these conditional interactions, the accuracy of metabolic risk prediction can be significantly enhanced, separating patient populations into more precise risk strata.

To process the large-scale data comparisons generated by integrating genomic and clinical datasets, the adoption of Artificial Intelligence (AI) and Machine Learning (ML) algorithms becomes imperative. Traditional statistical methods frequently fail to capture the non-linear relationships and epistatic effects (gene-gene interactions) that characterize complex metabolic pathways. ML algorithms, such as Random Forests, Support Vector Machines (SVM), and Deep Learning neural networks, excel at identifying hidden patterns within such heterogeneous datasets.

In the context of PTP1B risk stratification, ML models can be trained using electronic health records (EHR) and biobank data encompassing the genetic profiles of T2DM patients. These algorithms can weight the relative contribution of each *PTPN1* SNP alongside fluctuations in clinical parameters over time. The ultimate output of this processing is a dynamic predictive model capable of providing personalized risk scores that update in real-time as a patient's lifestyle or clinical interventions change.

The implementation of AI in this risk modeling also facilitates the discovery of new T2DM sub-phenotypes. Through unsupervised clustering techniques, patients can be grouped into unique metabolic clusters, such as a "genetically-mediated high PTP1B insulin resistance" group versus an "age-related inflammation-driven insulin resistance" group. Identifying these sub-phenotypes is a crucial step in shifting the diabetes management paradigm away from a one-size-fits-all approach toward data-driven precision medicine.

The ultimate goal of integrating PTP1B genetic data and clinical factors is to facilitate the application of precision medicine in the future management of T2DM. Through accurate risk stratification, clinicians can identify individuals within ultra-high-risk cohorts well before macrovascular or microvascular damage occurs. Early interventions for these groups can be designed to be more aggressive and targeted.

For individuals identified as having high risk predominantly driven by the *PTPN1* genetic factor, prevention strategies can focus on specific lifestyle interventions known to modulate PTP1B expression, such as periodic caloric restriction or resistance training. Additionally, this stratification guides the intensity of clinical surveillance, ensuring that patients with high integrative risk scores receive more frequent screening schedules for complications (such as retinopathy and nephropathy) compared to those in low-risk strata.

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Therapeutically, mapping the PTP1B genetic profile assists in predicting the efficacy of existing antidiabetic medications. For example, the effectiveness of insulin sensitizers like metformin or thiazolidinediones (TZDs) may vary depending on the baseline level of PTP1B activity determined genetically. Consequently, precision medicine not only minimizes trial-and-error in drug prescribing but also reduces the risk of adverse effects and optimizes healthcare resource utilization.

Given its central role as a negative regulator of insulin and leptin signaling, PTP1B has stood as a primary target in antiobesity and antidiabetic drug discovery for over two decades. Various PTP1B inhibitors, including both synthetic compounds and natural product derivatives, have been developed and evaluated in preclinical models. Inhibition of PTP1B has been proven to restore insulin sensitivity, enhance GLUT4 translocation, and normalize glucose tolerance without triggering dangerous hypoglycemic episodes.

However, the development of early-phase PTP1B inhibitors faced immense selectivity challenges. The catalytic site of PTP1B exhibits extremely high sequence homology (up to 85%) with other phosphatases, particularly T-cell protein tyrosine phosphatase (TCPT / PTPN2). Non-specific inhibition of TCPT can trigger severe systemic toxicity and immune dysfunction, as TCPT plays a crucial role in hematopoiesis and immune homeostasis. These functional failures historically halted the progress of several drug candidates during early-stage clinical trials.

To overcome these selectivity barriers, modern drug design strategies have shifted from targeting the active site (orthosteric) toward developing allosteric inhibitors. Allosteric inhibitors bind to less conserved sites located away from the main catalytic pocket, inducing conformational changes that selectively inactivate the enzyme without disrupting TCPT function. Recent advances in computational chemistry and molecular dynamics modeling have yielded several novel allosteric compounds demonstrating high efficacy and vastly improved safety profiles in animal models, reviving hopes for the future therapeutic commercialization of PTP1B.

Implementing a genomics-based integrative strategy in a developing nation like Indonesia is confronted by massive infrastructural and socioeconomic challenges. The scarcity of large-scale molecular laboratory facilities capable of performing routine, cost-effective genotyping serves as a primary bottleneck outside of major academic research centers. Furthermore, genetic testing is not currently covered under the national health insurance system (BPJS Kesehatan), rendering it an exclusive, secondary service accessible only to higher-income demographics.

Sociodemographic challenges also arise from Indonesia's highly heterogeneous population structure, which comprises hundreds of distinct ethnic groups with unique genetic backgrounds. Current global genomic reference data is heavily skewed toward Caucasian populations; thus, Polygenic Risk Scores developed in Western cohorts often lack accuracy when applied directly to local populations. Substantial investment in nationwide genetic association studies, such as local biobank initiatives, is urgently required to map *PTPN1* SNPs that are truly representative of Indonesian ethnicities.

Despite these significant hurdles, the long-term prospects for implementation remain highly promising. Driven by the falling costs of global genome sequencing and increasing government awareness regarding the blueprint for health technology transformation, the gradual integration of genomic data is highly achievable. Collaborative efforts between research institutions, universities, and the Ministry of Health to build risk stratification algorithms tailored to the clinical-genomic characteristics of the Indonesian population will serve as a vital foundation for preventing a future explosion of T2DM cases.

In conclusion, Protein Tyrosine Phosphatase 1B (PTP1B) is proven to be a critical regulatory node bridging the metabolic signaling of insulin and leptin with the clinical manifestations of Type 2 Diabetes Mellitus and obesity. Integrating genomic data from the *PTPN1* gene with conventional clinical determinants like age, sex, and body mass index opens a new paradigm in patient risk stratification. Utilizing artificial intelligence technologies and developing selective allosteric inhibitors completes this precision medicine ecosystem to deliver truly personalized interventions. Future research must focus on the functional validation of *PTPN1* genetic variants specific to Southeast Asian populations, particularly in Indonesia, alongside conducting prospective clinical trials to establish the cost-effectiveness of this integrative predictive model. Through sustained research commitment and the reinforcement of biomedical infrastructure, the transition from reactive diabetes management to genome-based predictive prevention strategies can be achieved, ultimately reducing the global and national socio-medical burden of T2DM.

This paper aims to review the potential for integrating PTP1B genomic data with clinical factors in the risk stratification of insulin resistance in patients with T2DM. In this regard, a comprehensive overview of the relationship between genetic and clinical factors as well as future research directions in the development of risk prediction and more precise therapeutic application**.**

2. Research Methods

The method used in this article is a scoping review. Literature searches were conducted systematically through PubMed, Scopus, and Google Scholar using keywords related to PTP1B, genomics, insulin resistance, and clinical factors, with publication limits of 2016–2025. From the initial search results, 105 articles were obtained from PubMed, Scopus, and Google Scholar. After the removal of duplication (n = 27), a total of 78 articles were selected

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through title and abstract screening, with 41 articles eliminated as irrelevant. Out of 37 full-text articles assessed, 30 were excluded due to failure to meet the inclusion criteria, leaving 7 articles for the final analysis. The selection process is carried out according to the guidelines. Data extraction included study identity, study design, population characteristics, genotyping methods, PTP1B variations, insulin resistance outcomes, as well as clinical factors such as body mass index, age, and HbA1c. Quality assessments are conducted to ensure validity and reliability, and only studies of medium to high quality are included in the analysis.

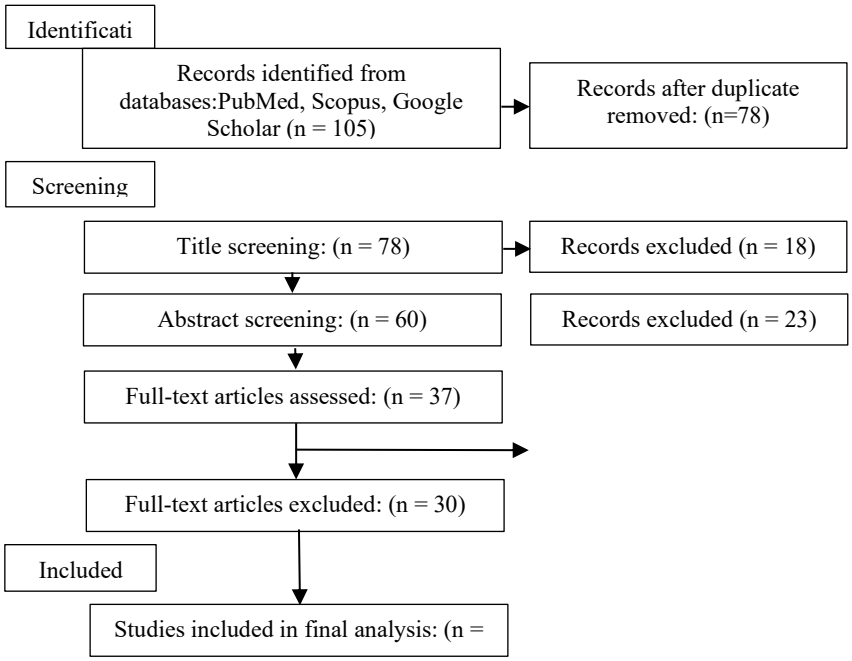


Figure 2. Flowchart of literature selection and screening.

3. Results and Discussions

Based on the results of the literature selection using the PRISMA method, 8 articles were obtained that met the inclusion criteria and were used in the analysis. The main characteristics of the included studies are presented in Table 1.l.

Table 1. Study Results

Research Title	Design and Subject	Key Parameters and Results
"Single nucleotide polymorphism and promoter methylation analysis of protein tyrosine phosphatase 1B in patients with myeloproliferative neoplasms" (Zhou *et al*., 2025)	Case-control A total of seven SNPs were identified, including rs1885177, rs2230604, rs75493894, rs2282147, rs2082849587, rs1364576352, and novel SNP + methylation; 96 patients, 50 controls Location : China	Significant SNP frequency differences and PTP1B promoter hypermethylation in patients
"Association between PTPN1 polymorphisms and obesity-related phenotypes in European adolescents: influenceofphysical activity" (Salazar-Tortosa *et al*., 2023)	Cross-sectional; rs6067472, rs10485614, rs2143511, rs6020608, rs968701; 1057 remaja Location : Europe	Associated with decreased adiposity, influenced by physical activity
"Asociation of protein tyrosine phosphatase 1B gene polymorphism with the effects of weight reduction therapy on bodyweight and glycolipid profiles in obese patients Association of PTPN1polymorphisms with breast cancer risk: A case-control study in Chinese females" (Yamakage *et al*., 2021)	Prospektive cohort; RS3787348, RS6067484; 447 patients Location: Japan	SNP rs3787348 is associated with weight loss therapy response

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"Analysis of the association between PTPN1 gene polymorphisms (rs941798 and rs914458) and type 2 diabetes in families from Lima – Peru" (Sánchez-Castro *et al*., 2019)	Family-based case-control; rs941798, rs914458; 23 family trios Location: Peru	No significant association was found between SNP and T2DM after statistical correction
"The Role of Polymorphism Gly972Arg IRS-1 Gene and C981T PTP-1B Gene on Insulin Resistance Young Adult Subjects with Low Birth Weight History" (Permana *et al*., 2018)	Cohort; C981T; 97 cases, 97 controls Location: Indonesia	Insulin resistance (HOMA-IR) No significant association with insulin resistance (HOMA-IR)
"Association of Protein Tyrosine Phosphatase 1B (PTPN1) Gene Polymorphisms (1023C>A and 467T>C) With Type 2 Diabetes: A Case Control Study" (Mackawy & Alfarag Ahmed, 2015)	Case Control; 1023C>A, 467T>C; 100 cases, 80 controls Location: Egypt	1023C>A is significantly related to T2DM and HOMA-IR

Based on an analysis of eight included studies, the genetic variation of PTP1B showed a diverse role in insulin resistance and related metabolic conditions. Some studies reported significant associations, such as the 1023C>A variant associated with T2DM and HOMA-IR, with the SNP rs3787348 influencing the response of weight loss therapy. In addition, certain genetic variations are also associated with a decrease in adiposity affected by physical activity, suggesting the presence of a genetic interaction and environmental factors. Another study showed the involvement of epigenetic mechanisms through hypermethylation of the PTP1B promoter in relation to changes in SNP frequency. However, not all studies found a significant association, where some polymorphisms such as rs941798, rs914458, and C981T showed no association with insulin resistance or T2DM after further analysis. Overall, these findings suggest that PTP1B's role in insulin resistance is complex and is influenced by a combination of genetic, epigenetic, and clinical factors (Mackawy & Alfarag Ahmed, 2015; Yamakage et al., 2021; S. Huang et al., 2019; Permana et al., 2018; Salazar-Tortosa et al., 2023; Zhou et al., 2025; Sanchez-Castro et al., 2019).

The increasing prevalence of T2DM globally reflects a major challenge in public health, which is not only influenced by lifestyle changes but also by complex biological factors. The surge in the number of cases suggests that conventional approaches based on common risk factors have not been sufficient to explain the variation in vulnerability between individuals. In this context, understanding genetic factors is becoming increasingly important, especially in identifying individuals at high risk for insulin resistance. The biological variation underlying differences in metabolic responses between individuals indicates the need for a more targeted and character-based approach (Galicia-García *et al*., 2020; Ahmed & Mohammed, 2025; Piko *et al*., 2022; Tang *et al*., 2025).

At the molecular level, the PTP1B gene functions as a negative regulator of the insulin signaling pathway by promoting the dephosphorylation of insulin receptors and insulin receptor substrates. This activity has an impact on decreasing the transmission of insulin signals and leads to reduced cell sensitivity to insulin. The central role of PTP1B in the regulation of glucose homeostasis and energy makes it an important component in the pathogenesis of insulin resistance (Fakhruzain & Tuba, 2024).

Analysis of genetic variation suggests that some polymorphisms, such as 1023C>A and rs3787348, have a relationship with insulin resistance and metabolic response, including an association with T2DM and the effectiveness of weight loss therapy. In contrast, other variations such as rs941798, rs914458, and C981T did not show significant associations. These differences in findings reflect that the genetic contribution of PTP1B is not homogeneous, but rather is influenced by the biological and methodological context of each study. Thus, the interpretation of the results cannot be done in isolation, but it is necessary to consider the overall pattern of the findings (Mackawy & Alfarag Ahmed, 2015; Yamakage *et al*., 2021; Permana *et al*., 2018; Salazar-Tortosa *et al*., 2023).

Further, the integration of clinical factors provides a more comprehensive understanding of the relationship between genetic variation and insulin resistance. The expression of genetic effects can be influenced by several modulating factors, including age, body mass index, physical activity, and other metabolic conditions. Variations such as rs6067472, rs2143511, and rs968701 show a relationship with adiposity that depends on the level of physical activity, confirming that the genetic effects are contextual. This suggests that insulin resistance is the result of an interaction between genetic predispositions and individual physiological conditions, so a single factor-based approach is not enough to explain the complexity that occurs (S. Huang *et al*., 2019; Sánchez-Castro *et al*.,

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2019; Zhou *et al*., 2025; S. Huang *et al*., 2019; Mackawy & Alfarag Ahmed, 2015; Sanchez-Castro *et al*., 2019; Yamakage *et al*., 2021; Zhou *et al*., 2025).

In addition to genetic variation, the involvement of epigenetic mechanisms such as hypermethylation of the PTP1B gene promoter suggests the presence of additional regulation that affects gene expression. This mechanism allows for changes in gene activity without changes in DNA sequences, thus explaining phenotypic variation in individuals with similar genetic backgrounds. The existence of this regulatory layer reinforces that insulin resistance is determined not only by SNP variation, but also by the dynamics of gene expression that are influenced by the environment and the internal conditions of the body (Fakhruzain & Tuba, 2024).

The integration between genetic variation, clinical factors, and epigenetic mechanisms provides a solid foundation in the development of insulin resistance risk stratification approaches. By combining the various dimensions of such data, it is possible to identify individuals based on a more specific and accurate risk profile. This approach has direct implications for the development of more personalized management strategies, where interventions can be tailored to the biological characteristics of each individual. In this context, the use of the PTP1B gene is relevant in supporting the development of precision medicine in T2DM, especially in an effort to increase the effectiveness of prevention and individualized risk-based therapies.

4. Conclusion

Genetic variations in the PTP1B gene, such as 1023C>A, rs6067472, rs2143511, rs968701, and rs3787348, show roles in modulating insulin resistance, adiposity, and metabolic response, although not all variants show consistent associations. Clinical and environmental factors, including body mass index and physical activity, contribute to these influences, as well as epigenetic mechanisms in the form of promoter methylation, which together reflect the complexity of insulin resistance pathogenesis in T2DM. Therefore, the integration of genetic variation, clinical factors, and epigenetics has the potential to improve the accuracy of insulin resistance risk stratification and support the development of precision medicine approaches, although further research with a stronger design and a wider population is still needed.

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