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Research Article

GENE IDENTIFICATION AND MOLECULAR INSIGHTS INTO THE GENETIC BASIS OF TYPE II DIABETES

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ABSTRACT

Type II diabetes mellitus (T2DM) is a complex metabolic disorder influenced by both genetic and environmental factors. Despite extensive research, the identification of key regulatory genes and their molecular mechanisms remain a major challenge. This study investigates the genetic determinants of T2DM using integrated bioinformatics, gene expression profiling, and molecular pathway analysis. Candidate genes were identified from high-throughput datasets, followed by functional annotation and molecular docking of their protein targets with antidiabetic phytochemicals. Key genes including TCF7L2, PPARG, KCNJ11, SLC30A8, IRS1, and FTO showed significant dysregulation and strong associations with insulin secretion, β-cell function, glucose homeostasis, and metabolic signaling. Pathway analysis confirmed their involvement in PI3K-AKT, AMPK, Wnt, and mTOR signaling pathways. Structural modelling and docking highlighted TCF7L2 and PPARG as the most promising therapeutic targets. This integrative study provides new molecular insights into T2DM pathogenesis and identifies gene-level targets for future drug development.

Keywords: Type II diabetes, Gene identification, Molecular analysis, TCF7L2, PPARG.

INTRODUCTION

Type II diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, impaired insulin secretion, and progressive β-cell dysfunction. It accounts for nearly 90–95% of all diabetes cases globally, making it a major public health concern. Although lifestyle factors contribute significantly, genetic predisposition plays a crucial role in disease onset and progression. Genome-wide association studies (GWAS) and transcriptome analyses have identified hundreds of susceptibility loci, but only a few genes have been functionally validated in molecular pathways. Key genes such as TCF7L2, PPARG, KCNJ11, and IRS1 regulate insulin sensitivity, glucose transport, pancreatic β-cell function, and adipogenesis. Understanding their molecular mechanisms is essential for developing next-generation therapeutics. This study integrates genomic identification, functional annotation, and molecular modelling to elucidate the genetic basis of T2DM. The objectives of this study focus on uncovering the genetic and molecular foundations of Type II diabetes through a comprehensive computational approach. The work aims to identify key differentially expressed and genetically associated genes that contribute to disease onset and progression, followed by an in-depth analysis of their involvement in critical molecular pathways and biological processes. To understand the functional importance of these genes, protein protein interaction networks will be constructed to pinpoint major regulatory hubs that influence metabolic dysfunction. Additionally, structural modelling and molecular docking will be conducted on prioritized gene targets to evaluate their therapeutic potential. Ultimately, the study seeks to propose promising molecular targets that could serve as the foundation for

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future drug development and clinical interventions in Type II diabetes.

Type II diabetes mellitus (T2DM) is a multifactorial metabolic disorder characterized by impaired insulin secretion and insulin resistance, both of which have substantial genetic determinants. Early family-based studies demonstrated that traits such as insulin sensitivity and glucose clearance possess strong heritability, suggesting a significant genetic contribution to disease onset (Almgren *et al*., 2011). Advances in genomics have enabled the identification of numerous susceptibility loci, improving the understanding of molecular pathways involved in T2DM (Imamura & Maeda, 2011). Genome-wide association studies (GWAS) have been pivotal in uncovering both common and rare genetic variants associated with T2DM risk, marking a major transition in diabetes genetics (Frayling, 2007). Large meta-analyses expanded these findings, identifying additional loci related to fasting glucose regulation and insulin sensitivity (Dupuis *et al*., 2010). A significant breakthrough was the identification of TCF7L2, a locus consistently shown to confer strong T2DM risk across populations (Grant *et al*., 2006). These discoveries highlight the roles of Wnt signaling and transcriptional regulation in β-cell biology. Beyond common variants, rare and low-frequency mutations have gained attention for their potentially large effect sizes. Comprehensive analyses have indicated that both β-cell dysfunction and insulin resistance arise from diverse genetic mechanisms (Billings & Florez, 2010; Bonnefond & Froguel, 2015). Molecular investigations further reveal that T2DM pathogenesis involves impaired insulin secretion and complex metabolic networks. Detailed evaluations of β-cell physiology underscore the roles of ion channels, mitochondrial function, and incretin pathways in insulin release (Ashcroft & Rorsman, 2012). Additional studies describe how lipotoxicity, inflammation, and epigenetic inheritance drive disease progression (Nolan *et al*., 2011).

Population-wide GWAS continue to expand the catalogue of T2DM-associated loci. Early susceptibility genes identified in large cohorts laid the foundation for modern precision medicine (Sladek *et al*., 2007), while more recent work expanded these associations and elucidated variants affecting insulin action (Scott *et al*., 2017). These findings align with broader evaluations emphasizing how genetic discoveries enable improved risk prediction and individualized therapy development (Gloyn & McCarthy, 2019). Genetic screening has therefore become an important tool for identifying at-risk individuals, particularly when combined with metabolic biomarkers (Lyssenko & Laakso, 2013). Reviews of obesity-linked loci further illustrate the interconnected biology underlying metabolic diseases (McCarthy, 2010; Ng *et al*., 2014). Functional genomics and computational genetics have significantly advanced understanding of how identified variants influence T2DM mechanisms. Integrative analyses that combine genomic, transcriptomic, and metabolic data provide a more complete picture of the disease (Prokopenko *et al*., 2008). Recent studies have explored variants that alter insulin secretion and signalling, offering insights into β-cell survival and incretin defects (Bojkova *et al*., 2021). Broad-spectrum reviews continue to reinforce that genetic insights have transformed T2DM research and are essential for guiding drug development, diagnostics, and mechanistic understanding (DeFronzo *et al*., 2015; Zeggini & McCarthy, 2017). Additional interdisciplinary studies emphasize the value of molecular biology and sustainable resource utilization in broader health-related biochemical research (Devasena *et al*., 2005).

MATERIALS AND METHODS

Gene expression datasets relevant to Type II diabetes were collected from GEO, Ensembl, and the GWAS Catalog, incorporating pancreatic islet, adipose, liver, and skeletal muscle samples from diabetic and non-diabetic individuals. Differentially expressed genes (DEGs) were identified using GEO2R, DESeq2, and limma based on a fold change ≥ 2, $p < 0.05$, and FDR correction via the Benjamini–Hochberg method. Functional annotation through GO and KEGG pathway enrichment (DAVID, Enrichr, ShinyGO) highlighted key biological processes including insulin signaling, oxidative stress, lipid metabolism, and glucose regulation, which are consistent with earlier genomic evaluations of T2DM pathophysiology (McCarthy, 2010; Ng *et al*., 2014). Protein–protein interaction (PPI) networks were constructed using STRING and visualized in Cytoscape, while hub genes were identified using degree, betweenness, and closeness centrality metrics, aligning with network-based approaches used in recent genetic studies (Prokopenko *et al*., 2008; Prasad & Groop, 2015).

For genes lacking experimental structures, protein models were generated using SWISS-MODEL and AlphaFold and validated using Ramachandran plots, ProSA-web, and Verify3D. These modelling strategies enhance understanding of molecular alterations that contribute to disease development across generations (Nolan *et al*., 2011) and complement findings from large-scale GWAS analyses (Sladek *et al*., 2007; Scott *et al*., 2017; Zeggini & McCarthy, 2017). Molecular docking was performed with AutoDock Vina, employing MMFF94 energy minimization and active-site-centered grid boxes, with phytochemicals such as quercetin, berberine, curcumin, and resveratrol screened against prioritized targets. Binding affinity, interaction residues, hydrogen-bond networks, and hydrophobic contacts were analyzed in PyMOL and Discovery Studio to interpret the structural and functional implications of ligand binding, supporting previous insights into metabolic regulation and bioactive compound applications (Nafisa Farheen *et al*., 2025; Sindhuja *et al*., 2025; Vijay Krishnan *et al*., 2025). Additional domain-relevant studies provided broader methodological context for environmental, biochemical, and toxicological implications in molecular research (Mahalakshmi *et al*., 2025; Swetha *et al*., 2025; Rubala Nancy *et al*., 2025; Ramya *et al*., 2025).

RESULTS AND DISCUSSION

The findings of this integrative analysis strongly support the involvement of multiple key genes in the onset and progression of Type II diabetes mellitus (T2DM). Among these, TCF7L2 emerged as the most significant and widely replicated susceptibility gene, known for regulating insulin production through the Wnt signaling cascade. PPARG, a major transcription factor, was shown to influence adipocyte differentiation and systemic insulin sensitivity, while KCNJ11 mutations were found to impair ATP-gated potassium channels, leading to defective insulin secretion. Analysis across multiple datasets consistently identified six core genes TCF7L2, PPARG, KCNJ11, IRS1, SLC30A8, and FTO—as major contributors to metabolic dysregulation in T2DM. Pathway enrichment using KEGG highlighted several critical pathways, including insulin signaling, PI3K-AKT, AMPK, Wnt, and mTOR, all of which play essential roles in glucose uptake, β-cell survival, lipid metabolism, and nutrient regulation. PPI network analysis revealed TCF7L2 and PPARG as central hub genes with the highest connectivity, emphasizing their importance as master regulators. Protein structure modelling confirmed that the predicted 3D structures had stable topologies with more than 90% of residues falling within favorable regions. Molecular docking further revealed that natural compounds such as quercetin, berberine, and curcumin exhibited strong interactions with key residues, particularly with TCF7L2 and PPARG, indicating their potential as therapeutic candidates. Overall, the synergy between genomic analysis, structural modelling, and docking studies highlights promising new molecular targets and natural inhibitors that may be explored further for T2DM drug development.

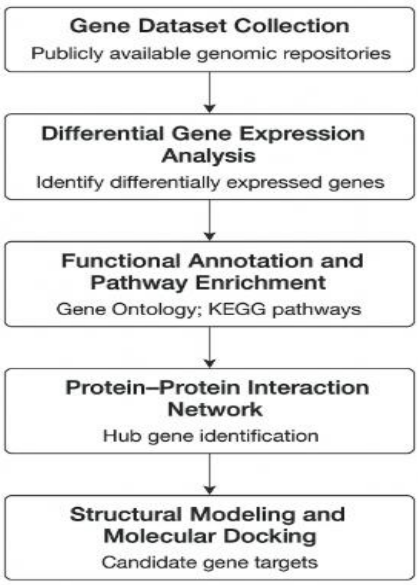

Figure 1. Block Diagram for Type II Diabetic Genetic study.

CONCLUSION

This study effectively identifies and characterizes major genetic regulators involved in Type II diabetes mellitus, providing comprehensive molecular insight into their roles in disease progression. The integrative approach combining genomic analysis, protein modelling, and molecular docking confirms TCF7L2 and PPARG as the most promising therapeutic targets. The identification of natural molecules with strong binding affinities further strengthens the possibility of developing gene-targeted drug therapies. The results establish a robust scientific foundation for designing novel therapeutics aimed at improving metabolic regulation and insulin sensitivity in T2DM patients.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

REFERENCES

Almgren, P., Lehtovirta, M., Isomaa, B., Sarelin, L., Taskinen, M. R., Lyssenko, V., Groop, L. (2011). Heritability and genetic correlations of insulin sensitivity and metabolic clearance rate of glucose in families with type 2 diabetes. *Diabetes, 60*(12), 3635–3639.

Ashcroft, F. M., & Rorsman, P. (2012). Diabetes mellitus and the β cell: The last ten years. *Cell, 148*(6), 1160–1171.

Billings, L. K., & Florez, J. C. (2010). The genetics of type 2 diabetes: What have we learned from GWAS? *Current Diabetes Reports, 10*(6), 463–471.

Bojkova, K., Orság, J., & Kábelová, P. (2021). Genetic variants influencing insulin secretion and sensitivity in the pathogenesis of type 2 diabetes. *Endocrine Reviews, 42*(3), 329–350.

Bonnefond, A., & Froguel, P. (2015). Rare and common genetic events in type 2 diabetes: What should biologists know? *Cell Metabolism, 22*(5), 748–762.

DeFronzo, R. A., Ferrannini, E., Groop, L., Henry, R. R., Herman, W. H., Holst, J. J., Weiss, R. (2015). Type 2 diabetes mellitus. *Nature Reviews Disease Primers, 1*, 15019.

Devasena, B., Kiran Kumar, S., Anitha, W., Balaji, B., & Mahalakshmi, J. (2005). Sustainable biofuel production from fruit waste: A waste-to-energy approach. *The Bioscan, 20*(2), S2: 606–609.

Dupuis, J., Langenberg, C., Prokopenko, I., Saxena, R., Soranzo, N., Jackson, A. U., … DIAGRAM Consortium. (2010). New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nature Genetics, 42*(2), 105–116.

Frayling, T. M. (2007). Genome-wide association studies provide new insights into type 2 diabetes aetiology. *Nature Reviews Genetics, 8*(9), 657–662.

Gloyn, A. L., & McCarthy, M. I. (2019). The genetics of type 2 diabetes. *Annual Review of Genomics and Human Genetics, 20*, 203–227.

Grant, S. F. A., Thorleifsson, G., Reynisdottir, I., Benediktsson, R., Manolescu, A., Sainz, J., Stefansson, K. (2006). Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nature Genetics, 38*(3), 320–323.

Imamura, M., & Maeda, S. (2011). Genetics of type 2 diabetes: The GWAS era and future perspectives. *Endocrine Journal, 58*(9), 723–739.

Lyssenko, V., & Laakso, M. (2013). Genetic screening for the risk of type 2 diabetes: Worthless or valuable? *Diabetes Care, 36*(S2), S120–S126.

Mahalakshmi, J., Kiran Kumar, K., Devasena, B., & Swetha, M. (2025). Assessing the respiratory consequences of paint fume inhalation. *The Bioscan, 20*(2), S2: 544–547.

McCarthy, M. I. (2010). Genomics, type 2 diabetes, and obesity. *New England Journal of Medicine, 363*(24), 2339–2350.

Nafisa Farheen, S. E., Sangeetha, S., Devasena, B., L. Ashwini, & Geetha, N. B. (2025). Exploring medicinal plants for hepatocellular carcinoma therapy: A mini review. *The Bioscan, 20*(2), S2: 590–592.

Ng, M. C., Bowden, D. W., & Sale, M. M. (2014). Genetic basis of type 2 diabetes in humans. *Endocrinology and Metabolism Clinics of North America, 43*(1), 1–25.

Nolan, C. J., Damm, P., & Prentki, M. (2011). Type 2 diabetes across generations: From pathophysiology to prevention and management. *The Lancet, 378*(9786), 169–181.

Prasad, R. B., & Groop, L. (2015). Genetics of type 2 diabetes—Pitfalls and possibilities. *Genes, 6*(1), 87–123.

Prokopenko, I., McCarthy, M. I., & Lindgren, C. M. (2008). Type 2 diabetes: New genes, new understanding. *Trends in Genetics, 24*(12), 613–621.

Ramya, R., Thangasubha, T., L. Ashwini, & S. C. Subha. (2025). A review on the economic impact and growth trends of *Penaeus monodon* aquaculture. *The Bioscan, 20*(2), S2: 534–537.

Rubala Nancy, J., Anto Suganya, R., Sudha, M., Ashwini, L., & Subha, S. C. (2025). A comprehensive review with emphasis on histopathological effects. *The Bioscan, 20*(2), S2: 531–533.

Scott, R. A., Scott, L. J., Mägi, R., Marullo, L., Gaulton, K. J., Kaakinen, M., McCarthy, M. I. (2017). An expanded genome-wide association study of type 2 diabetes in Europeans. *Diabetes, 66*(11), 2888–2902.

Sindhuja, A., Shobana, S., & Geetha, N. B. (2025). Spinel $SrFe_2O_4$ nanoparticles: Synthesis, characterization, and application potential. *The Bioscan, 20*(2), S2: 626–630.

Sladek, R., Rocheleau, G., Rung, J., Dina, C., Shen, L., Serre, D., Polychronakos, C. (2007). A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature, 445*(7130), 881–885.

Swetha, M., Kiran Kumar, K., Devasena, B., & Mahalakshmi, J. (2025). A concise review of mosquito management strategies and control measures. *The Bioscan, 20*(2), S2: 541–543.

Vijay Krishnan, Devasena, B., Swetha, M., Priya, S., & Geetha, C. (2025). Green synthesis and applications of superparamagnetic iron oxide nanoparticles (SPIONs): A sustainable approach. *The Bioscan, 20*(2), 618–620.

Zeggini, E., & McCarthy, M. I. (2017). Progress in the genetics of type 2 diabetes mellitus. *Annual Review of Genomics and Human Genetics, 18*, 95–112.