INTERNATIONAL JOURNAL OF APPLIED AND CLINICAL RESEARCH

IJACR

Research paper

Integrative Bioinformatic Analysis of TCF7L2 (Q9NQB0) Polymorphisms Associated with Type 2 Diabetes

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Abstract: Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder influenced by both genetic and environmental factors. Among the susceptibility genes, *TCF7L2* is one of the most significant contributors to insulin secretion and glucose metabolism. **Objective:** This study aimed to investigate the structural and functional impact of *TCF7L2* polymorphisms associated with T2DM using an integrated bioinformatics approach. **Methods:** Disease-associated genes were identified using DisGeNET and MalaCards databases, and overlapping genes were analyzed using Venny 2.1. Functional enrichment analysis was performed using ShinyGO to determine the biological roles of *TCF7L2*. A missense variant, c.4C>G (p.Pro2Ala), was selected from the gnomAD database for pathogenicity assessment. The deleterious nature of the variant was predicted using SIFT, PolyPhen-2, and MutationTaster. Three-dimensional structures of wild-type and mutant proteins were modeled using AlphaFold. Molecular docking with resveratrol was performed using AutoDock Vina to evaluate binding interactions. **Results:** Functional enrichment analysis indicated that *TCF7L2* is involved in insulin signaling, pancreatic β-cell development, and glucose metabolism pathways. The selected missense mutation was predicted to be deleterious by multiple *in-silico* tools. Molecular docking revealed stable ligand–protein interactions, with altered binding affinity and interaction profiles between wild-type and mutant proteins. **Conclusion:** The *TCF7L2* variant (p.Pro2Ala) may influence protein function and contribute to T2DM pathogenesis. Additionally, resveratrol demonstrated notable binding affinity toward *TCF7L2*, suggesting its potential therapeutic relevance.

Volume No 04, Issue 02, 2026

Received: 27th May 2026
Accepted: 14th June 2026
Published: 15th June 2026
Doi: https://doi.org/10.66222/IJACR.04.02.59

How to cite: Rohma, S. (2026). Integrative bioinformatic analysis of TCF7L2 (Q9NQB0) polymorphisms associated with type 2 diabetes. *International Journal of Applied and Clinical Research*, 4(02), 49–59
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Keywords: Type 2 diabetes mellitus; *TCF7L2* gene; missense mutation; bioinformatics analysis; molecular docking; protein structure modeling; resveratrol; insulin signaling pathway.

Introduction

Diabetes mellitus (DM), a chronic metabolic disease caused by abnormalities in insulin action, secretion, or both. It is among the most common non-communicable diseases worldwide. Protein, fat, and glucose metabolism are all impacted by diabetes mellitus If left untreated, it can lead to major problems such retinal, neuropathy, nephropathy, and cardiovascular disease. Urbanization, inactivity, and an increase in the number of obese individuals have all contributed to the rise in the prevalence of diabetes mellitus over time.(1)Diabetes is becoming more common, which is a serious public health issue, particularly in developing nations. According to recent studies, sedentary lifestyles, poor eating habits, and restricted access to healthcare services are contributing to the sharp increase in diabetes prevalence in nations like Pakistan. This increasing burden emphasizes the need for better illness management, early detection, and preventive measures.(2) The illness is a diverse collection of metabolic conditions that share chronic hyperglycemia as a common characteristic. Type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes mellitus, and other specialized types of diabetes are the primary categories of diabetes.(3) A metabolic condition called diabetes

mellitus is typified by consistently elevated blood sugar levels. Frequent urination, excessive thirst, and increased appetite are typical symptoms. Serious side effects include hyperosmolar coma and diabetic ketoacidosis may result if treatment is not received. The two main forms are Type 2 diabetes.(4)In people who are genetically predisposed, type 1 diabetes is an autoimmune condition brought on by T lymphocytes destroying pancreatic β-cells. HLA gene variations have been found to have strong correlations with illness risk, although non-HLA genes like INS, CTLA4, and PTPN22 also play a role. One of the most commonly heritable common disorders is T1D.(5) A prevalent metabolic condition, type 2 diabetes mellitus is brought on by decreased insulin-sensitive tissue response and decreased insulin release from pancreatic β-cells.(6) The risk of Type 2 Diabetes Mellitus is greatly increased by obesity and excess body fat, and the risk increases with body mass index. Thus, type 2 diabetes is becoming more common due to the global increase in obesity.(7) Insulin resistance, a disorder in which bodily tissues like muscle, liver, and adipose tissue do not react well to insulin, is one of the main causes of diabetes, especially type 2 diabetes. Persistent hyperglycemia is the result of decreased glucose absorption and increased glucose synthesis in the liver. It has been demonstrated that genetic differences increase the risk of developing diabetes by causing insulin resistance and pancreatic beta-cell malfunction.(8) Another important factor in the development of diabetes is genetic predisposition. Research shows that inherited genetic variations that affect insulin production and glucose metabolism significantly increase the chance of getting diabetes in people with a family history of the condition.(9)The transcription factor 7-like 2 (TCF7L2)(10) it is a transcription factor that binds to DNA via a high-mobility group (HMG) domain. It belongs to the T-cell factor/lymphoid enhancer binding factor family (TCF/LEF Due to its substantial genetic link with type 2 diabetes, the TCF7L2 gene has received a lot of attention. The TCF7L2 gene is a fundamental component of the Wnt signaling pathway, which was originally associated with the biology of development and consists of a complex network of interacting proteins with cellular intercommunications regulated at several levels, producing numerous consequences. Wnt network-related proteins, such TCF7L2, have been linked to a wide range of common diseases and cancer models, demonstrating the significance of this developmental route in the pathophysiology of human disorders.(11) Variants in the TCF7L2 gene were first linked to type 2 diabetic mellitus (T2D) in 2006 and colon cancer (CC) in 1999.The alleles rs7903146-T and rs12255372-T of the TCF7L2 single nucleotide polymorphisms (SNPs) have the highest odds ratio (OR) ~1.4 for T2D-risk.(12) Elevated blood glucose levels brought on by inadequate insulin production or compromised insulin activity characterize diabetes mellitus (DM), a chronic metabolic disease.1 About 537 million individuals worldwide are impacted. 10.2% by 2030 and 10.9% by 2045 are expected to be impacted. Type 2 diabetes-predisposing *TCF7L2* SNPs are associated with a higher percentage of residual insulin-containing cells (ICI%) in pancreases of donors (13) .

Methodology

Gene Identification and Selection for Type 2 Diabetes

Using extensive bioinformatics database mining, genes linked to Type 2 Diabetes Mellitus (T2DM) were found. The DisGeNET and MalaCards databases, which offer curated data on gene–disease associations gathered from experimental investigations, genome-wide association studies (GWAS), and biomedical literature, were the first sources of disease-associated genes. To find overlapping genes with strong connections with Type 2 Diabetes, the Venny 2.1 tool was used to compare the retrieved gene lists from both databases. ShinyGO, which combines gene ontology and pathway databases like KEGG (Kyoto Encyclopedia of Genes and Genomes) to find biological pathways strongly linked to the chosen genes, was used to perform functional enrichment analysis of the overlapping genes. Strong involvement of candidate genes in pathways linked to insulin secretion, glucose metabolism, and pancreatic β-cell function—all crucial mechanisms underpinning the development of Type 2 Diabetes—was found by the pathway enrichment analysis. Furthermore, the identified genes' functional roles and disease relevance were investigated by consulting the Online Mendelian Inheritance in Man (OMIM) database. TCF7L2 (Transcription Factor 7-Like 2) was chosen as the main gene of interest among the candidate genes since numerous genome-wide association studies and population-based genetic analyses have shown a high genetic relationship with type 2 diabetes (16, 17).

Variant Identification and Selection

The genomAD (Genome Aggregation Database), which has extensive human genetic variation data obtained from many populations, was consulted in order to find disease-relevant genetic variants within the TCF7L2 gene. Given that different ethnic groups can have varied genetic susceptibility patterns, special emphasis was paid to variations found in the South Asian population. The missense mutation c is one of the documented variations. The amino acid change of

proline to alanine at position 2 in the TCF7L2 protein sequence led to the selection of 4C>G (p.Pro2Ala) for additional study This missense variation may affect the encoded protein's structural stability and functional activity, which could lead to changes in glucose metabolism and an increased risk of Type 2 diabetes. Using MutationTaster, a prediction tool for assessing the possible disease-causing implications of genetic variants, the mutation was computationally injected into the wild-type nucleotide sequence (18, 19).

Pathogenicity Prediction of the Selected Variant

Several in-silico pathogenicity prediction methods were used to assess the possible functional implications of the chosen TCF7L2 variation. Based on sequence homology and evolutionary conservation across species, the Sorting Intolerant from Tolerant (SIFT) algorithm was employed to assess the likelihood that the amino acid alteration would impact protein function. Additionally, by considering the physicochemical variations between amino acids and the structural characteristics of the protein, Polymorphism Phenotyping version 2 (PolyPhen-2) was used to examine the potential structural and functional effects of the amino acid substitution. Additionally, the functional impacts of coding variations were predicted using FATHMM (Functional Analysis Through Hidden Markov Models) based on sequence conservation and hidden Markov model profiles. These computational techniques offered a thorough assessment of the chosen mutation's probable pathogenicity and its potential role in the pathophysiology of Type 2 Diabetes 3.4 Structure Prediction of Wild-Type and Mutant Proteins (20, 21).

Prediction of Wild-Type and Mutant Protein Structures

AlphaFold, a deep-learning-based protein structure prediction technology created by DeepMind, was used to predict the three-dimensional (3D) protein structures of both the wild-type and mutant TCF7L2 proteins to examine the structural implications of the chosen mutation. AlphaFold is frequently utilized in computational structural biology research and has shown impressive accuracy in predicting protein structures based just on amino acid sequences. The Protein Data Bank (PDB) format of the predicted structures made it possible for additional structural research and visualization. These structures were then utilized for stability analysis and molecular docking to assess the structural changes brought about by the mutation (22).

Ligand Selection for Molecular Docking

Ligands having established therapeutic significance in the treatment of Type 2 Diabetes were chosen for molecular docking research. Metformin and pioglitazone, two commonly prescribed antidiabetic medications, were selected for the docking investigations because of their proven functions in enhancing insulin sensitivity and controlling glucose metabolism. The PubChem database, which offers chemical structure and bioactivity data for a vast variety of chemicals, provided the three-dimensional structures of the ligands. After being downloaded in SDF format, these ligand structures were transformed into the proper forms for docking analysis. This is the ligand accession number(Resveratrol) (445154) (23).

Molecular Docking Analysis

MOE, a popular computational docking program made to forecast protein–ligand interactions and binding affinities, was utilized for molecular docking studies. The projected protein structures were constructed by eliminating water molecules, including polar hydrogen atoms, and allocating suitable atomic charges before docking In order to use AutoDock Vina docking simulations, the produced protein structures have to be translated into PDBQT format. To limit the docking search space and concentrate on biologically significant binding interactions, a grid box was created around the protein's estimated active binding domains. Several ligand binding postures were produced by the docking simulations, and matching binding affinity values, expressed in kcal/mol, were computed. Discovery studio was used to visualize the docking data, and the Protein–Ligand Interaction Profiler (PLIP), which is also carried out by MOE, was used to analyze the interactions between the protein and ligands, including hydrogen bonds and hydrophobic contacts (24, 25).

Protein–Ligand Interaction Analysis:

Using BIOVIA Discovery Studio, molecular docking analysis was performed to assess the interaction between TCF7L2 and resveratrol. The findings demonstrated sustained binding inside the anticipated TCF7L2 binding pocket via hydrophobic contacts and hydrogen bonding. Tyr137, Tyr140, Phe130, Leu143, and Gly145 were important interaction residues. Resveratrol may affect TCF7L2-related pathways implicated in glucose metabolism and Type 2 Dia-

betes Mellitus, according to the 2D and 3D interaction analyses that verified appropriate ligand accommodation and complex stability (26).

Results

Gene selectin and identification for type 2 diabetes

DisGeNET and MalaCards provided a list of genes linked to Type 2 Diabetes Mellitus (T2DM). The genes TCF7L2, KCNJ11, PPARG, SLC30A8, FTO, HHEX, CDKAL1, IGF2BP2, CDKN2A, MTNR1B, IRS1, GCK, GCKR, AKT2, WFS1, HNF1A, HNF4A, GLIS3, NOTCH2, and KLF14 were included in the DisGeNET dataset. TCF7L2, CTNNB1, WNT3A, WNT5A, LEF1, TCF7, AXIN1, AXIN2, GSK3B, DKK1, LRP5, LRP6, FZD1, FZD7, CCND1, MYC, GCG, INS, and PDX1 were all included in the MalaCards dataset. One overlapping gene, TCF7L2, was found between the two databases when these datasets were compared using Venny 2.1, suggesting a high degree of confidence in its relationship with T2DM.

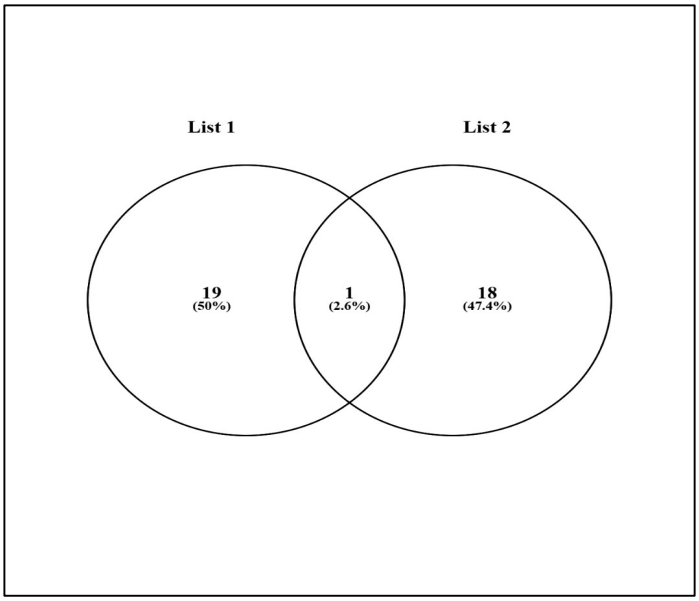

Figure 1: The analysis further revealed 19 unique genes in List 1 and 18 unique genes in List 2.

KECG pathway analysis

The pathway analysis produced by ShinyGO revealed that the chosen genes have a major role in the development of pancreatic β-cells, insulin signaling, and glucose metabolism pathways linked to Type 2 Diabetes Mellitus (T2DM). The graphic illustrates how important transcription factors and signaling molecules, including PDX1, HNF1A, HNF4A, and INS, interact to regulate β-cell development and insulin generation. These results imply that changes in these genes may interfere with normal insulin control and lead to the onset of type 2 diabetes.

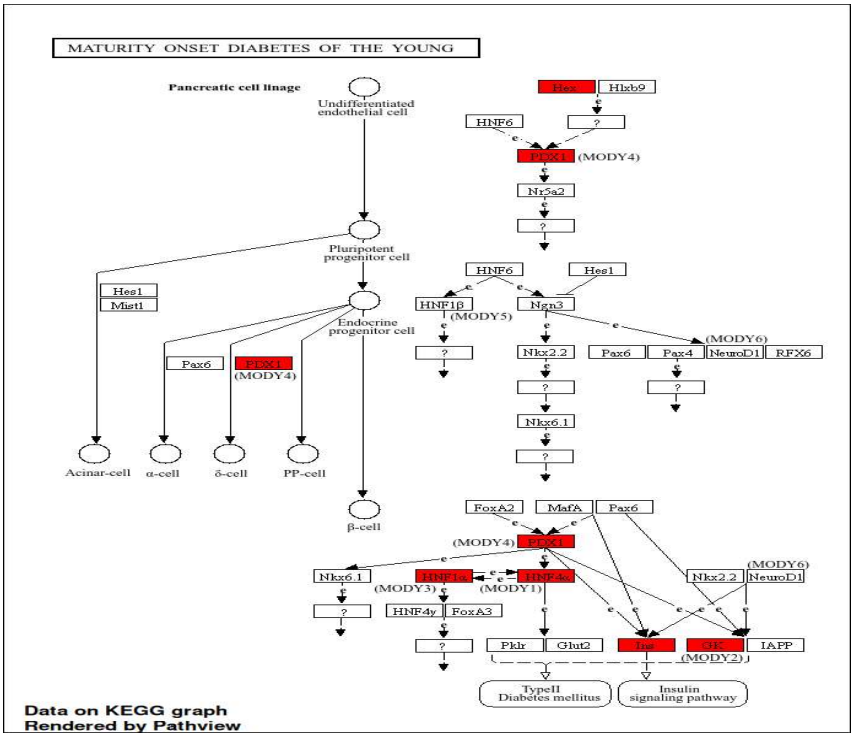

Figure 2: KECG pathway analysis illustrates the involvement of TCF7L2 gene

Mutation pathogenesis analysis

Protein function was negatively impacted by the TCF7L2-c.4C>G (p.Pro2Ala) mutation, according to in silico investigation of its pathogenic potential.

Table 1. Computational prediction of the pathogenicity of the c.4C>G (p.Pro2Ala) mutation in the TCF7L2 gene

Tool	Prediction	Score
SIFT	Not Tolerated (Deleterious, low confidence)	0
PolyPhen-2	Probably Damaging	0.998
Mutation Taster	Disease Causing	High Confidence

Molecular docking analysis

The wild-type TCF7L2 protein's molecular docking investigation showed that the ligand successfully bound within the anticipated active site cavity. Several significant amino acid residues, such as Arg105, Leu106, Gly108, Val110, Val112, Cys113, Ala135, and Ala136, exhibited persistent interactions with the ligand. The binding pocket analysis showed that the ligand was properly accommodated inside the protein surface, indicating complex stability and favorable protein–ligand affinity. These interactions—primarily hydrophobic and hydrogen bonding interactions—may enhance the ligand's biological activity and suggest that it may be useful in treating Type 2 Diabetes Mellitus. The ligand was successfully bound into the target protein's anticipated active pocket, according to molecular docking research. Several amino acid residues, such as Arg105, Asn104, Trp156, Leu158, and His147, engaged in ligand interaction, indicating the creation of stable protein–ligand complexes.

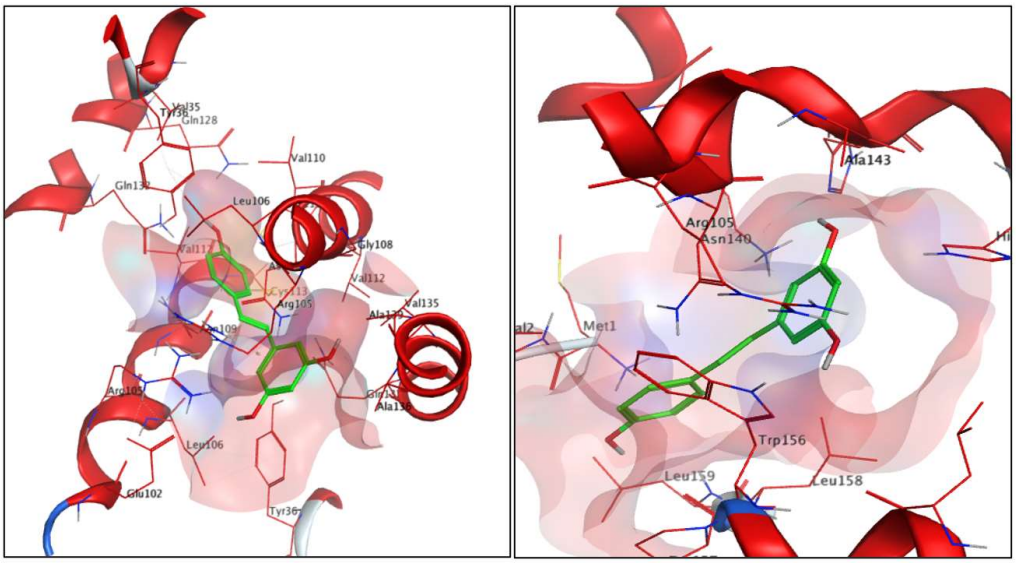

Figure 3: (A) Molecular docking of wild type sequence. (B) molecular docking of mutant type sequence.

Mutant and wild-type TCF7L2 complexes differ according to the docking analysis. A more stable ligand-binding conformation was suggested by the wild-type protein's slightly higher final docking score (S score = -6.0725) and lower RMSD refinement value. Stronger contact and placement energies during docking were indicated by the mutant complex's much lower E_place, E_score1, and E_refine energies.

Table 2: Comparison analysis of mutant and wild type sequence of protein

Parameter	Mutant Average	Wild Type Average
S Score	-5.24	-5.02
RMSD Refine	1.93	1.45
E_conf	-46.30	-34.99
E_place	-74.00	-1.35
E_score1	-10.35	-6.44
E_refine	-23.70	-6.54
E_score2	-5.24	-5.02

Mutant and wild type ligand interaction

The chosen ligand produced multiple significant contacts within the target protein's active binding pocket, indicating sustained molecular binding and possible biological activity, according to the 2D ligand–protein interaction study. Key amino acid residues such as Arg105, Glu102, Tyr36, Asn109, Gln132, Cys113, Val110, Val112, Val135, Ala136, and Leu106 were shown to be involved in the interaction map. Among these, Arg105 demonstrated a strong arene–cation interaction with the ligand's aromatic ring, which greatly aided in the stabilization of the ligand inside the binding cavity. Residues like Val110, Val112, Val135, Ala136, and Leu106 were shown to exhibit hydrophobic interactions, indicating advantageous nonpolar contacts that improve binding affinity. The ligand was surrounded by polar residues, such as Gln128, Gln132, Asn109, Tyr36, and Cys113, which may help with further hydrogen bonding and electrostatic stabilization. The probability of hydrogen bond formation within the active site is further supported by the ligand's hydroxyl groups. Overall, the interaction profile indicates that the ligand may have promising inhibitory potential against the target protein and shows strong binding compatibility with the receptor.

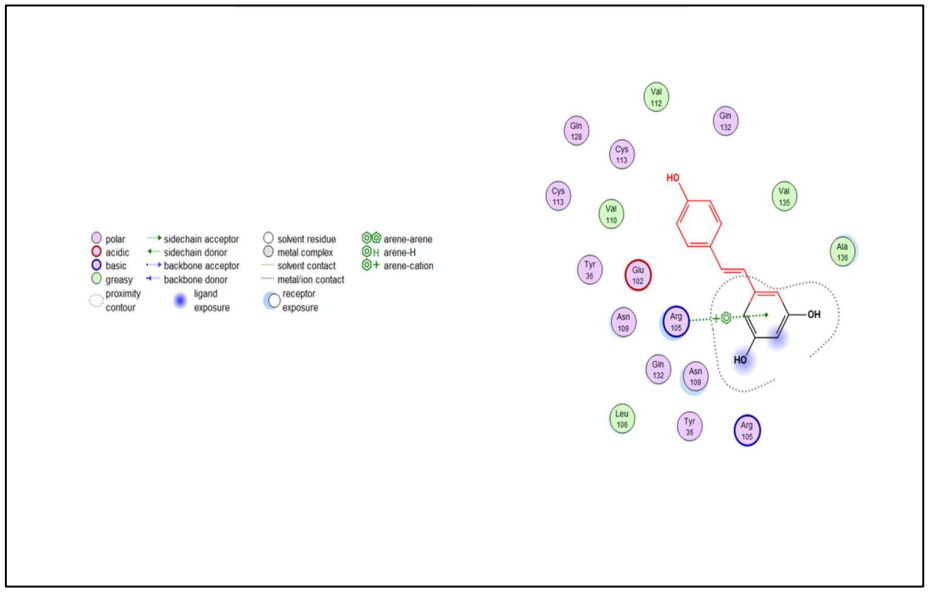

Figure 4: wild type ligand interaction. (Resveratrol) (445154)

The ligand was well accommodated within the target protein's active binding pocket, according to the 2D ligand–protein interaction study, which also created a number of significant molecular interactions that support the complex's stability. Key amino acid residues surrounding the ligand, such as Arg105, Glu102, Tyr36, Asn109, Gln128, Gln132, Cys113, Val110, Val112, Val135, Ala136, and Leu106, were discovered by the interaction map. Among these, Arg105 demonstrated a potent arene–cation interaction with the ligand's aromatic ring, which is crucial for keeping the ligand stable inside the receptor cavity. Additionally, hydrophobic interactions with residues like Val110, Val112, Val135, Ala136, and Leu106 were noted, suggesting advantageous nonpolar contacts that improve the ligand's binding affinity. Asn109, Gln128, Gln132, Tyr36, and Cys113 are examples of polar residues that were found near the ligand and may aid in further electrostatic interactions and hydrogen bond stabilization. Additionally, the ligand structure's hydroxyl functional groups imply the potential for hydrogen bond formation with neighboring residues, strengthening the connection overall. Multiple stabilizing interactions show that the ligand has good binding compatibility with the active site and could be an effective target protein inhibitor.

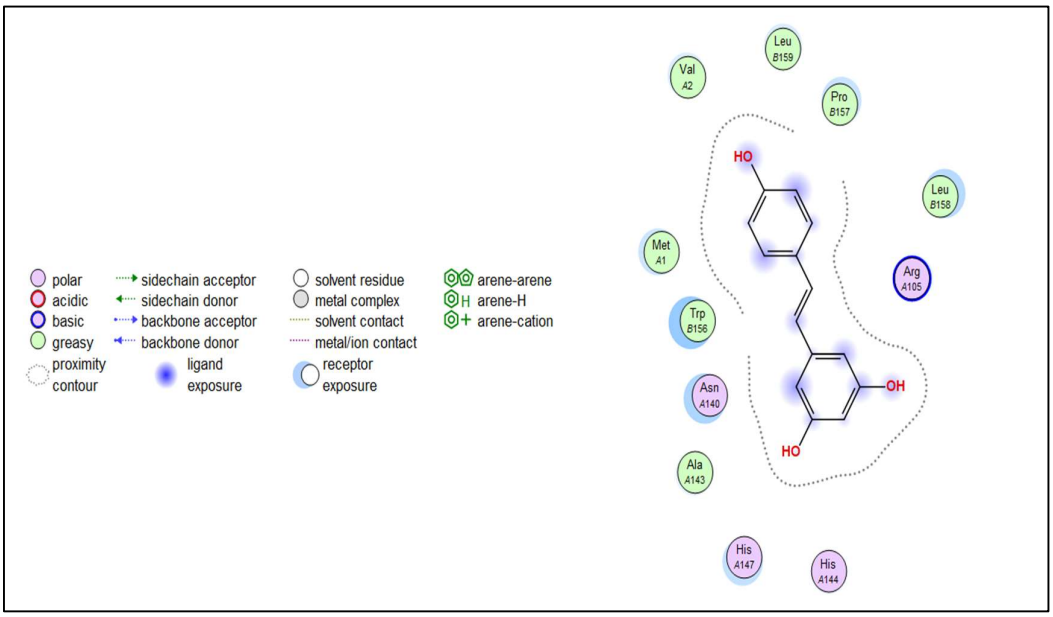

Figure 6: Mutant type ligand interaction

Protein and ligand interaction

Stable binding contacts inside the receptor's active region were shown by the molecular docking analysis of resveratrol with the TCF7L2 protein. Resveratrol generated numerous substantial interactions with important amino acid residues, such as Asn140, Arg105, His147, Ala143, Trp156, and Met1, according to both 3D and 2D interaction analyses. Strong polar contacts that support ligand stabilization were indicated by the observation of conventional hydrogen bonds with Asn140 and Arg105. Furthermore, the ligand's binding affinity was reinforced by carbon hydrogen bonding with His147. The stability of the ligand–protein complex was improved by hydrophobic interactions, such as Pi–Pi T-shaped interaction with Trp156 and Pi–Alkyl interaction with Ala143. Additionally, a Pi–Cation interaction involving Met1 was found, indicating further electrostatic stabilization in the binding pocket. All things considered, the interaction profile shows that resveratrol has a good binding affinity for the TCF7L2 protein and could function as a possible therapeutic inhibitor through stable molecular interactions.

Discussion

The current study investigated the relevance of TCF7L2 polymorphisms in the pathophysiology of Type 2 Diabetes Mellitus using an integrative bioinformatics method. TCF7L2 was shown to be a frequent overlapping gene across DisGeNET and MalaCards through comparative study of disease-associated datasets, suggesting a substantial correlation with T2DM risk. TCF7L2 is one of the strongest genetic risk factors associated with Type 2 Diabetes in a variety of populations, according to prior genome-wide association studies. The significance of the TCF7L2 gene in glucose metabolism and insulin secretion pathways was originally highlighted by Grant et al.'s report that variations in this gene dramatically raise the risk of type 2 diabetes.(27)The Wnt signaling pathway, which controls glucose homeostasis, insulin secretion, and pancreatic β-cell proliferation, depends on the TCF7L2 gene. Changes in this route may hinder the synthesis of insulin and lead to insulin resistance, two of the main pathogenic processes that underline type 2 diabetes. According to Del Bosque-Plata et al., deregulation of TCF7L2 expression contributes to the development of diabetes by influencing β-cell malfunction and glucose intolerance. Additionally, TCF7L2 polymorphisms are closely linked to decreased insulin secretion and an elevated risk of developing type 2 diabetes in the future, as shown by Lysenko et al.(17)In the present investigation, the missense mutation c.For pathogenicity analysis, 4C>G (p.Pro2Ala) was chosen. The mutation was projected to be harmful and disease-causing by computational prediction methods like SIFT, PolyPhen-2, and MutationTaster. The SIFT score indicated intolerance to amino acid replacement, however the PolyPhen-2 score of 0.998 indicated a likely detrimental influence on protein structure and function. Similar research has shown that missense mutations affecting highly conserved sites can change the biological activity, stability, and folding of proteins, ultimately interfering with cellular signaling pathways related to glucose metabolism. According to Adzhubei et al., harmful missense mutations often impact intermolecular interactions and protein structure, resulting in functional impairment.(28)Stable contacts between TCF7L2 and resveratrol within the active binding cavity were found using molecular docking research with AutoDock Vina. Significant residues of amino acids, such as Arg105, Asn140, Trp156, and His147, engaged in hydrophobic interactions and hydrogen bonding, suggesting complex stability and advantageous ligand accommodation. A naturally occurring polyphenolic molecule, resveratrol is well known for its antidiabetic and antioxidant properties. Resveratrol enhances insulin sensitivity, lowers oxidative stress, and modifies glucose metabolism pathways, according to earlier research. The strong binding affinity observed in this study suggests that resveratrol may influence TCF7L2-mediated signaling pathways and could potentially serve as a therapeutic candidate for T2DM management. Saleem et al. reported similar results, using integrated in-silico methods to identify phytochemical compounds that target TCF7L2.(29)

Conclusion

To sum up, this integrative bioinformatics work demonstrated how important the TCF7L2 gene is to the pathophysiology of Type 2 Diabetes Mellitus (T2DM). TCF7L2 was found to be a common overlapping gene that is substantially linked to diabetes susceptibility through comparative analysis utilizing DisGeNET and MalaCards. Its participation in insulin production, glucose metabolism, and pancreatic β-cell regulatory pathways was further shown by functional enrichment analysis. Several computational methods suggested that the chosen missense mutation c.4C>G (p.Pro2Ala) would be harmful and cause disease, indicating a possible impact on protein stability and function. When compared to the wild-type protein, structural modelling and molecular docking investigations showed that the mutation changed docking stability and ligand-binding interactions. Furthermore, resveratrol showed sustained binding

associations with TCF7L2, suggesting that it may have therapeutic value in modifying TCF7L2-related diabetes pathways. Overall, the results support the use of computational methods for identifying pathogenic variations and possible therapeutic targets in diabetes research and offer insightful information about the molecular pathways underlying type 2 diabetes.

Limitation

Without experimental or clinical validation, this study was restricted to computational and in-silico analyses. Bioinformatics methods were used to anticipate the effects of the TCF7L2 c.4C>G (p.Pro2Ala) variation, which may not accurately reflect real biological situations. Furthermore, even though Type 2 Diabetes Mellitus is a complicated multifactorial disease, only one variation and a small number of ligand interactions were examined. Additional in vitro, in vivo, and clinical research is required to establish the therapeutic potential of resveratrol and corroborate these findings.

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