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Protein Signaling As A Prospective Target For Insulin Resistance Treatment

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Abstract
Type 2 diabetes mellitus (T2DM) usually begins when protein signaling is disrupted, leading to insulin resistance. The study seeks to find out what role specific proteins such as PI3K, IGF-1, GRB2and GLUT4, also study the role of IRS-1 and GSK-3β genes in insulin resistance and also examine any possible genetic variations related to these pathways. Samples of blood taken from 100 patients were obtained at Al Wafaa Center for Diabetes and Endocrine Gland Diseases in Mosul between October 2024 and January 2025. There were four different sample groups: healthy persons as control, persons with insulin resistance only, persons with insulin resistance and diabetes finally, persons with diabetes alone without insulin resistance. Each group were divided into two age groups 10-35 years and 36-65 years. Determining the concentration of each protein was done by ELISA method and DNA was extracted and sequenced to assess changes in the genes. The results pointed to a significant decrease in PI3K and IGF-1 levels, also to significantly increases in GRB2 and GLUT4, showing that they are involved in insulin resistance. Besides, analysis of the GSK-3β and IRS-1 genes confirmed that they were present in every sample, along with finding new genetic variations may links to insulin resistance and diabetes, it can be considered this signals as promising goals for detect insulin resistance in people with T2DM.
Keywords: *PI3K, IGF-1, GRB2, GLUT4, IRS-1, GSK-3β*

Introduction:

People with type2 diabetes mellitus (DM) have consistently high levels of blood sugar [1, 2]. The worldwide incidence of T2DM shows an ongoing substantial increase because more than 400 million individuals now face this condition the predominant consequence of insulin resistance is T2DM [3].
Insulin resistance, identified as an impaired biologic response to insulin stimulation of target tissues, primarily involves liver, muscle, and adipose tissue. Insulin resistance impairs glucose disposal, resulting in a compensatory increase in beta-cell insulin production and hyperinsulinemia. The metabolic consequences of insulin resistance can result in hyperglycemia, hypertension, dyslipidemia, hyperuricemia, elevated inflammatory markers, endothelial dysfunction, and a prothrombotic state. Among these, the progression to T2DM is predominant, typically preceding its onset by 10 to 15 years [4]. Nutrient consumption by cells in response to normal and elevated insulin concentrations becomes abnormal in insulin resistance which disrupts glucose uptake and metabolic equilibrium. Increasingly, evidence points to abnormalities in protein signaling pathways as central drivers in the pathogenesis of insulin resistance [5].Insulin resistance requires immediate treatment strategies that target the molecular causes because this dangerous pattern continues to worsen. The promising targets in medical research today include protein signaling pathways since these pathways control essential processes of glucose metabolism and cellular energy balance and lipid homeostasis[6].Insulin signaling helps to regulate how many glucose a cell takes in and how it works. When insulin binds to the receptor, the receptor phosphorylates IRS-1 which launches a sequence that activates PI3K. The activation of PI3K causes PIP3 to be produced which brings Akt to the site, where it blocks GSK3β and helps glycogen be built [7]. Akt facilitate the translocation of glucose Transporter Type 4 (GLUT4) to the plasma membrane so glucose can be transported into the cell [8]. Additionally, growth factor receptor bound protein-2 (GRB2) helps control the body's ability to process insulin as well as develop insulin resistance. Many structures and mechanisms involved in diabetes and related complications are tied to problems with GRB2 which is a chief adaptor protein [9]. While glucose metabolism together with insulin sensitivity depends significantly on Insulin-like Growth Factor 1 Receptor (IGF-IR). IGF-IR displays structural and functional

relationships resembling the insulin receptor and controls pathways from insulin signaling. Scientific research indicates that altered activity of IGF-1 leads to insulin resistance which typically gets evaluated through the HOMA-IR. Diminished IGF-1 activity results in increased HOMA-IR markers which shows a clear link between IGF-1 dysfunction and insulin sensitivity impairment [10].Dysfunction with these molecules result in insulin resistance which is central to type 2 diabetes. Knowing what they are role is key to finding useful therapeutic approaches [7].Our study aims to explore protein signaling such as PI3K, IGF-1, GRB2 and GLUT4 as a target for insulin resistance treatment, in addition to study IRS-1 and GSK3 genes to determine whether they are related to genetic variation that could be linked to the previous proteins or insulin resistance resulting from diabetes.

Case Study

Blood samples were taken from 100 patients at Al Wafaa Center for Diabetes and Endocrine Gland Diseases in Mosul, patients were examined by physicians, research project number 2024182 received approval on 10 October 2024 and samples were collected under the supervision of a field samples were gathered in a period from October 2024 to January 2025. Samples were divided into four distinct groups consisting of 30 healthy individuals and 30 patients with insulin resistance together with another group of 30 patients who had both insulin resistance and diabetes, and 10 patients with type 2 diabetes without insulin resistance, and each group underwent additional age-based categorization for metabolic assessment into two age groups. (10–35) years and (36–65) years.

Collection of Blood Sample

Five ml of venous blood was drawn from these patients and divided into two groups; the first 2ml component was put into tubes containing EDTA anticoagulant to extract DNA, and the second 3ml was put into gel tubes. The blood was allowed to coagulate in the tubes for an half an hour before the blood was centrifuged for ten minutes at a speed of 3000 cycles per minute to extract the blood serum for the protein measurement.

Proteins Measurement

Concentration of proteins was assessed using kits from Sunlong Biotech Co., Ltd, China by ELIZA microplate photometer HiPo MPP-96 Bio San, Lithuania. From the labs of collage of science, university of Mosul.

DNA Extraction

The blood obtained for the project was used to make Genomic DNA using a kit prepared by Gene Aid according to how the company recommended [11].

1- Take a tube containing your blood, add the RBC Lysis Buffer, let it lie until the blood separates, spin in the centrifuge and save the bottom pellet while removing the top clear liquid.

2- Distribute the Cell Lysis Buffer into the tube after that, vortex to mix the materials, put the tube in a 60ºC oven and occasionally change its position with added RNase A.

3- Combine the pellet with Protein Removal Buffer, shake on a vortex mixer and then centrifuge. If the pellet is loose, you should put the mixture in ice.

4- Remove the supernatant, add isopropanol, spin again in the centrifuge, wash the tube surface two times with ethanol and dry the DNA pellet outside air.

5- Once your DNA is mixed with the solution, slowly heat it to 60ºC to allow your eluted DNA to gather up.

Determination of the Concentration and Purity of DNA.

The purity and concentration of DNA were determined using a Nano Drop equipment provided by the English company Bio Drop. The device was calibrated to zero with TE solution, then 1 microliter of DNA was introduced to quantify the concentration in (ng/µL) [12].

GSK-3β Gene Amplification and Electrophoresis

The extracted DNA used for PCR analysis of GSK-3β gene by using DNA primers shown in Table 1. The Thermal Cycler carried out the same sequence for each sample, starting with 3 minutes of denaturation in 95 °C. amplification steps required thirty five cycles after one-minute denaturation at 95 °C, forty-five seconds at 55 °C for annealing and a last step of extension holding at 72 °C for one minute. Afterwards, the slides was left in the AT solution for 5 more minutes at 72 °C. Products of the reaction were separated using gel electrophoresis, then stained with a safe red dye and viewed with UV light while in storage conditions.

IRS-1 gene amplification and electrophoresis

Detection of the IRS-1 gene polymorphism was achieved using PCR and the following primers from Table 1. It took 3 minutes to perform denaturation at 95 °C at the first stage. The process is made up of 35 cycles, including 30-second denaturation at 95 °C, 45-second annealing at 35 °C, 1 minute extension at 72 °C and a finishing 3-minute extension at 72 °C to amplify. Agarose gel analysis of the PCR products was done with a 2% agarose solution. Then safe red dye stained the sample and viewed under UV light at room temperature.

Table1: The primer sequencing employed to amplify genes GSK3β& IRS-1

Primer	Function	size	Sequence 5'-3'	Reference
F	Amplification of GSK3	270bp	5′ GACGTCCGTGATTGGCTC 3′	[13]
R			5′ AGCCCAGAG CCCTGTCAG 3	
F	Amplification of IRS	250bp	5'-TGGCGAGGTGTCCACGTAGC-3'	[14]
R			5'-CTTCTGTCAGGTGTCCATCC-3'	

Statistical Analysis

The data were analyzed according to the system of simple and universal experiments using a completely randomized design. The different information was significantly distinguished by different letters of the alphabet and performed by Duncan's test, one-way ANOVA at value of $P \leq 0.05$ by SPSS version 26 [15].

RESULTS AND DISCUSSION

Table 2 and 2 shown a significant decrease in each of PI3K and IGF-IR proteins in all of patients groups in compared to control group, it also show a significant increase in GRB2 and a slightly decrease in GLUT4

Table2: Effect of diabetes type 2 and insulin resistance on protein levels

Groups / parameters	Control	Patients		
		IR	Diabetes	IR& Diabetes
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
PI3K (pg/ml)	467.71±139.5^{a}	252.42±32.0^{b}	220.3±19.3^{b}	221.4±22.6^{b}
IGF-1(pg/ml)	913.2±163^{a}	456.3±32.2^{b}	414.7±24.9^{b}	303.7±40.6^{c}
GRB2(Pg/ml)	348.62±37.5^{c}	3075±297^{b}	13402±45.8^{a}	3396±248^{b}
GLUT4(µg/L)	28.55±1.83^{a}	25.4±4.3^{a}	27.05±3.2^{a}	27.31±2.72^{a}

*Different letters means there is a significant difference between values according to Duncan test.
** The values are means ± standard deviation (SD)

Table3: Effect of diabetes type 2 and insulin resistance on protein levels according to age factor

Groups / Parameters	Age	Control	Patients		
			IR	Diabetes	IR& Diabetes
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
PI3K(pg/ml)	(10-35)	329.32±54.44^{b}	248.5±8.49^{cd}	198±12.72^{e}	234.1±9.19^{cde}
	(36-65)	606.1±25.0^{a}	255.6±17.63^{c}	249±24.7^{cd}	210.4±29.3^{de}
IGF-1(pg/ml)	(10-35)	754.9±49.2^{b}	459.0±29.9^{c}	356.1±28.8^{d}	277±13.4^{e}
	(36-65)	1068.3±179.0^{a}	450.5±42.3^{c}	469.6±45.77^{c}	331.1±7.2^{d}
GRB2(pg/ml)	(10-35)	344.72±28.4^{d}	3039.3±259^{c}	13435±26.94^{a}	3798±142.1^{b}
	(36-65)	352.5±47.5^{d}	3112.6±292^{c}	13370±36.76^{a}	3114.3±386.35^{c}
GLUT4(µg/L)	(10-35)	26.24±1.96^{a}	25.3±4.3^{a}	29.1±0.24^{a}	28.7±0.08^{a}
	(36-65)	29.9±1.0^{a}	25.42±4.9^{a}	25±3.6^{a}	26.9±3.01^{a}

*Different letters means there is a significant difference between values according to Duncan test.

** The values are means ± standard deviation (SD)

Regarding GRB2 levels a significant increase in diabetic patients reinforce its involvement in insulin resistance development along with secondary diabetic complications and the reason behind this elevation in GRB2 levels is that in the insulin cascade of signaling, GRB2 is a bridging adaptor protein. It is associated with phosphorylated IRS1 and mediates downstream signaling through MAPK pathway which, in its overactivity redirects the signaling into other pathways - outside the crucial PI3K/AKT pathway through which glucose translocation must occur in the presence of GLUT4 [16].Our results align with [16] and their study about the role of GRB2 in diabetes, diabetes complications and related disorders, they found that GRB2 is present at much higher levels in patients with carotid atherosclerosis and type 2 diabetes mellitus, pointing to its value as a predictor. [17] they found that lowering the levels of GRB2 boosts the body's response to insulin by reducing IRS-1 serine phosphorylation and leading to more glucose uptake by insulin in mice and muscle cells, these findings align with our results shown in table 1 and 2 suggesting a noticeable increasing in GRB2 levels in insulin resistant and T2DM.Another study by

[18] administered GRB2 as a negative regulator to insulin signaling, they pointed that Serum GRB2 positively correlated with the level of C-reactive protein and interleukin-6 that were raised in T2DM patients (than in the healthy population) and their levels rose higher in patients with T2DM with carotid atherosclerosis. As for aging effect on GRB2 levels show a non-significant effect except in diabetes with insulin resistance group where it shows a significant decrease in advanced age and this align with [16] where they found that age has a negative correlation with GRB2. PI3K result show declining activity of PI3K occurs due to various conditions present in both insulin resistance alongside diabetes. the chronic high insulin exposure triggers Phosphatase and Tensin Homolog (PTEN) upregulation to create insulin resistance because PTEN functions as a negative PI3K pathway regulator, When PTEN functions at elevated levels it reduces PI3K/Akt signaling thereby blocking insulin's ability to transport glucose thus increasing metabolic problems [19]. And this agreed with a 2024 clinical trial by [20] showed

that shortly after giving the PI3K inhibitor to healthy adults, the population develops acute insulin resistance. This gives first hand evidence of the critical role played by PI3K as regards insulin sensitivity.Lower levels of IGF-1 are connected to a greater degree of insulin resistance, according to [10] showing that patients with this condition had significantly less IGF-1 than those who did not have it. It has been shown that resistance to insulin and the control of glucose can change IGF-1 values in T2DM patients. And this decrease in IGF-1 levels implying its involvement in insulin resistance and poor glycemic control and this results are in agreement with [21] on regulation of insulin resistance by targeting the insulin-like growth factor 1 receptor with microRNA-122-5p in hepatic cells which found that IGF- 1 concentration significantly reduced in a number of studies on type 2 diabetes mellitus (T2DM) and the condition of insulin resistance.

Furthermore the study results agreed with [22] on insulin signaling and GLUT4 trafficking in insulin resistance, who explained the reasoning for the reduction of GLUT4 levels is because of the poor insulin signaling pathway and GLUT4 trafficking. The proper function of GLUT4 proteins guarantees insulin-controlled glucose absorption in both skeletal muscle and adipose cells. Insulin resistance interferes with GLUT4 membrane translocation yet metformin-based therapies increase both GLUT4 levels and translocation function that eventually improves insulin sensitivity, which explain the nearly preserved levels of GLUT4 serve as an explanation for their minimal reductions [23]. Another study of [24] reveals the effect of insulin is to spread GLUT4 along the membrane, but in the case of insulin resistance, GLUT4 sometimes clusters together, which in turn reduce the level of GLUT4.

Molecular Study Results

The results of theGSK-3β gene, as shown in figure (1), indicate that base pair bands appeared at 270bp in all samples included in the study. These samples belong exclusively to the control group, group exhibiting resistance, the group of diabetes patients, as well as the group with both diabetes and resistance.

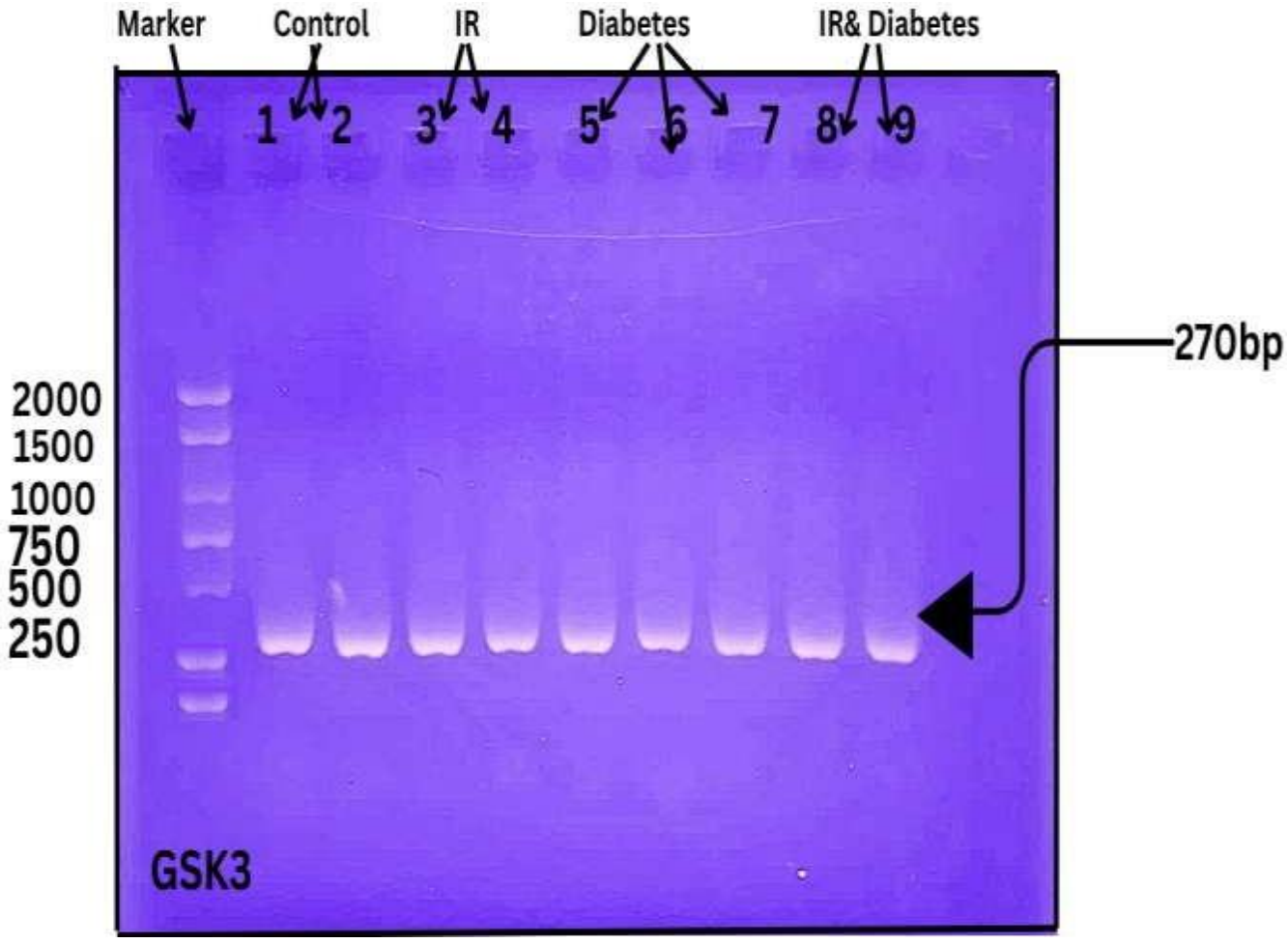

Figure 1 : PCR products of the GSK3β genes in 270 bp, M is the volume of 2000 bp

Additionally, the results shown in figure (2) indicate that the bands of the IRS-1 gene were observed at 250bp in all samples included in the study

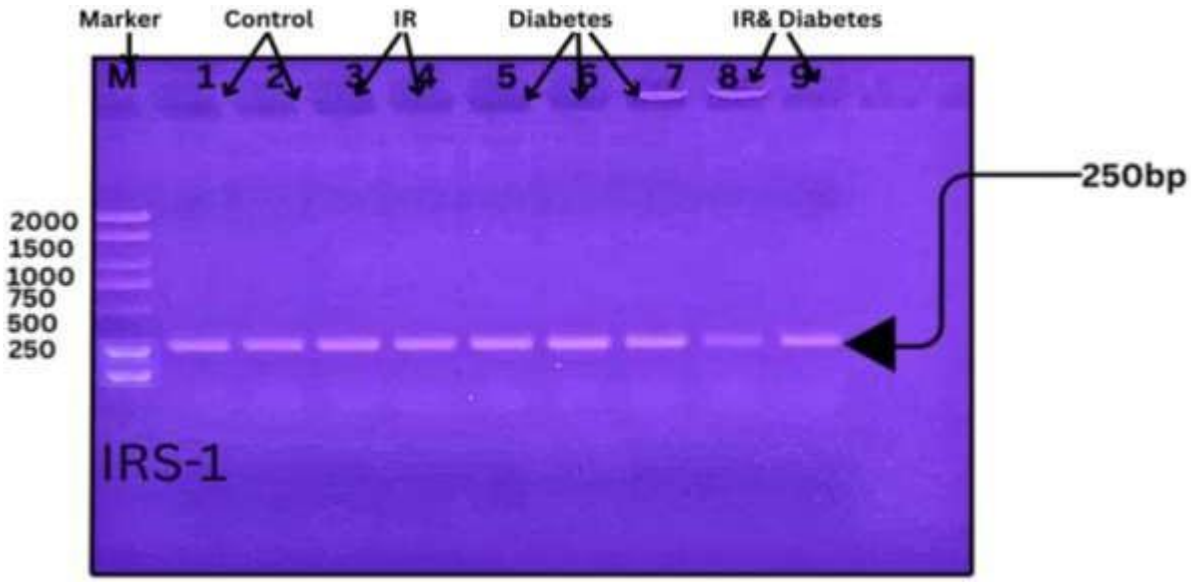

Figure 2: PCR products of theIRS-1 genes in 250 bp, M is the volume of 2000 bp

DNA Sequencing

As shown in the DNA pictures (Figures 3,4 and 5), the results revealed a strong 100% match between the nucleotide sequences of GSK3β and IRS-1 from the samples and the same genes provided on the National Center for Biotechnology Information (NCBI). The main reason for doing this test was to verify that the primers belongs to the same genes and to look for variations that could influence their functioning or play a role in the development of the disease. The study recorded four new genetic variation in Mosul city at NCBI, three of them belong to GSK3β with the identification numbers PV468254.1, PV468255.1, PV468256.1, belongs to insulin resistance, diabetes with and without insulin resistance, as for the fourth genetic variation belongs to IRS-1 gene by the number PV468257.1, belong to insulin resistance group.

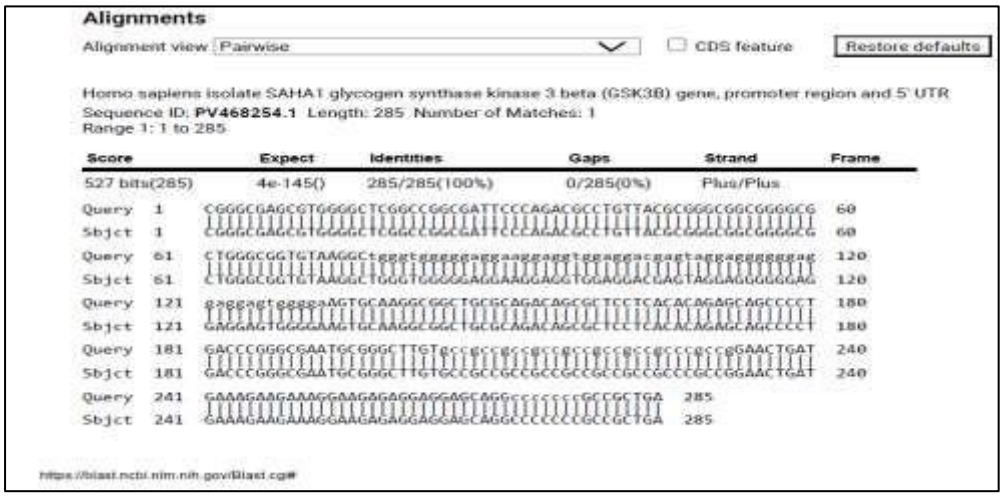

Figure (3) The alignment of the gene GSK3β gene to the nucleotide sequences of the NCBI belongs to IR Group

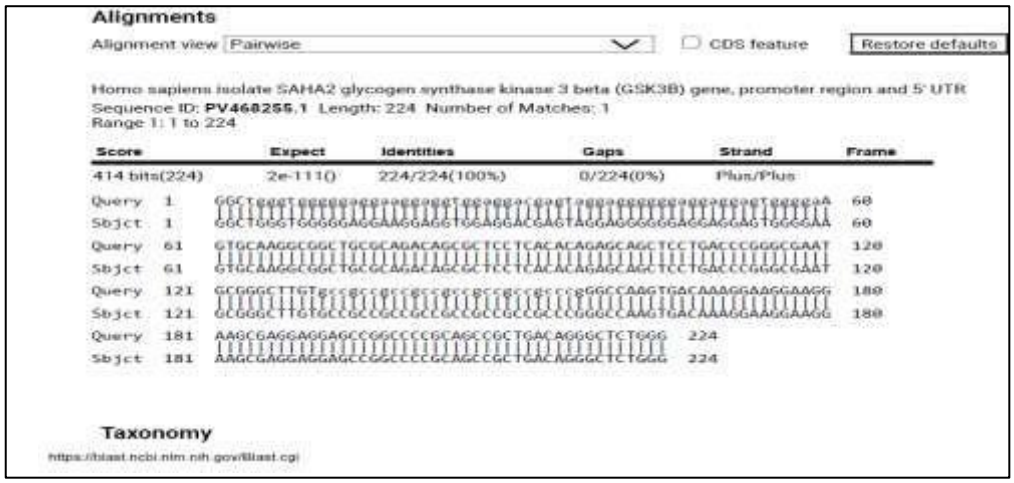

Figure (4) The alignment of the gene GSK3β gene to the nucleotide sequences of the NCBI belongs to IR& diabetes groups

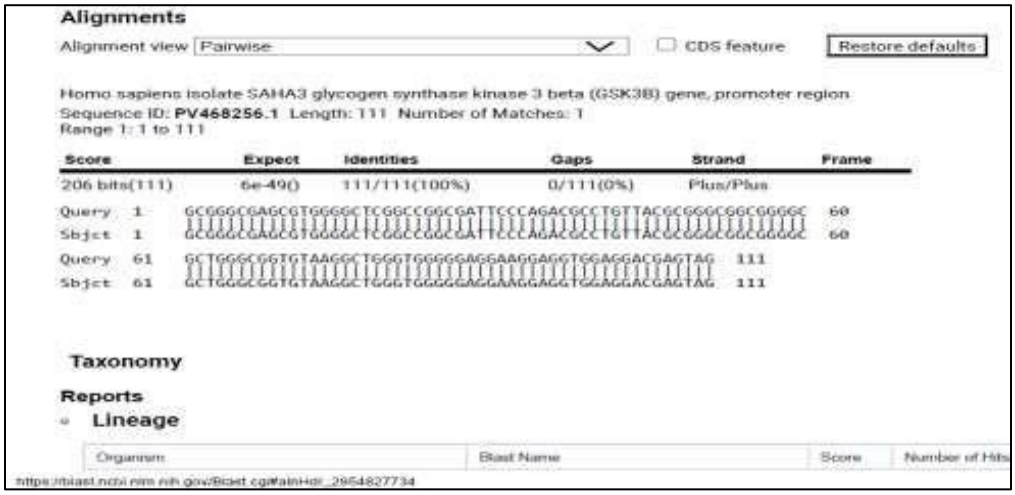

Figure (5) The alignment of the gene GSK3β gene to the nucleotide sequences of the NCBI belongs to diabetes group

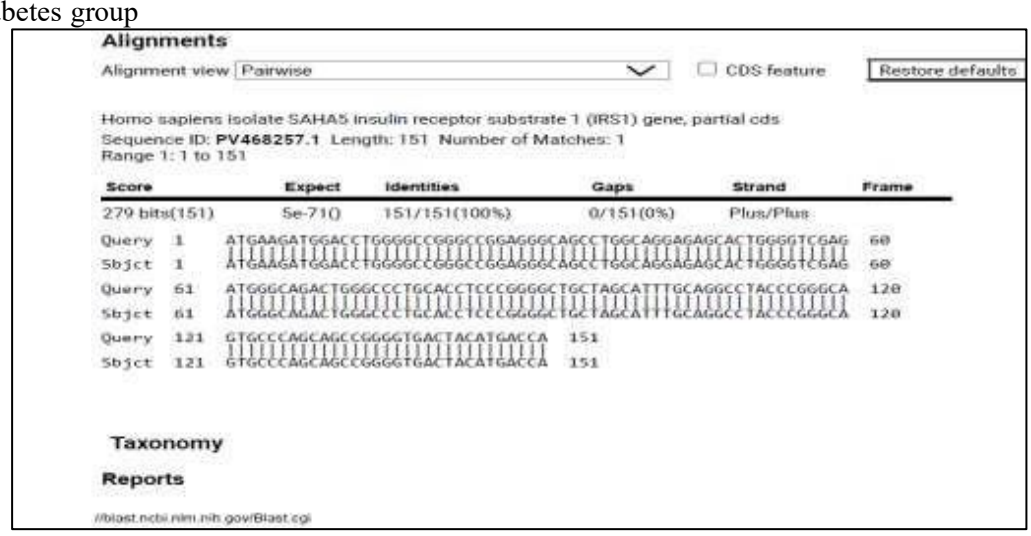

Figure (6) The alignment of the gene IRS-1 gene to the nucleotide sequences of the NCBI belongs to IR group

GSK3β turn out to be active in every sample, though a genetic variation that might indicate a mutations in the gene are linked to insulin resistance as well as diabetes, whether or not insulin resistance is present. It seems that how GSK3β works is linked to genes that play a role in insulin signaling and diabetes and this aligns with the study of [25], it explore how the activity of glycogen synthase kinase-3 (GSK-3) affects insulin resistance and type 2 diabetes. All the samples revealed GSK3β gene expression with no obvious differences between those with diabetes and those without which support our findings. The research demonstrates that an increased level of GSK3β activity intensifies insulin resistance because it obstructs glycogen synthesis resulting in reduced glucose storage [26] which mentioned that a high expression of GSK-3β was correlated with a decrease in insulin sensitivity.The GSK3β gene encodes glycogen synthase kinase 3 beta (GSK-3β), a crucial enzyme that influences β-cell negatively it is important for how β-cells function and for maintaining proper blood glucose. GSK3β takes part in glucocorticoid-related death of beta cells and blocks insulin secretion regulates insulin signaling [27].As regarding to IRS-1 [28] illustrate that insulin resistance does not influence gene expression in skeletal muscle which found that no clear differences in IRS-1 levels in skeletal muscle have been found between insulin-sensitive and insulin-resistant people while [29] find that The IRS-1 genetic variation directly influences insulin sensitivity levels since diabetic patients show greater prevalence compared to nonsusceptible individuals which found IRS-1 genetic factor may be a significant genetic determinant for IR in T2DM patients during severe/acute-phase hyperglycemia. A variety in the IRS1 gene has been found to be connected with both insulin resistance which lead to T2DM. Mutations within the IRS1 gene can make its structure weak and disrupt its ability to help with insulin signaling [30]. Another study on gestational diabetes

[14] Suggest that a mutation in IRS-1 gene can make insulin and its receptors not function properly which might lead to gestational diabetes, and the importance of IRS-1 lies in which insulin signaling is initiated by IRS1.

CONCLUSION

This research emphasize on the role of protein signaling in the pathogenesis of insulin resistance and Type 2 Diabetes Mellitus. The result obtained may enhance the possibility of using protein signaling also the genetic variation as an option to differentiate between individuals with diabetes with or without insulin resistance.

REFERENCES

1. Ghali, N. Q.; & Al-Ali, Z. A. R. (2024). Evaluation of Glucose, 8-isoprostane, and Some Reproductive Hormones Levels in Women with Obesity, Type 1 Diabetes and Hyperprolactinemia. Rafidain Journal of Science, 33(3), 8–19. https://doi.org/10.33899/rjs.2024.184531.
2. Al-Juwary, R., Al-Hayali, H.,2025, "Obesity and Insulin Resistance ", Rafidain Journal of Science, 34(1), 100–109. https://doi.org/10.33899/rjs.2025.186499
3. Wolosowicz, M.; Prokopiuk, S., & Kaminski, T. W. (2022). Recent Advances in the Treatment of Insulin Resistance Targeting Molecular and Metabolic Pathways: Fighting a Losing Battle? Medicina, 58(4), 472. https://doi.org/10.3390/medicina58040472
4. Nolan, C. J.; & Prentki, M. (2019). Insulin resistance and insulin hypersecretion in the metabolic syndrome and type 2 diabetes: Time for a conceptual framework shift. Diabetes and Vascular Disease Research, 16(2), 118–127. https://doi.org/10.1177/1479164119827611
5. Chandrasekaran, P.; & Weiskirchen, R. (2024). Cellular and Molecular Mechanisms of Insulin Resistance. Current Tissue Microenvironment Reports, 5(3), 79–90. https://doi.org/10.1007/s43152- 024-00056-3
6. Pei, J.; Wang, B.; & Wang, D. (2022). Current Studies on Molecular Mechanisms of Insulin Resistance. Journal of Diabetes Research, 2022, 1–11. https://doi.org/10.1155/2022/1863429.
7. Le, T. K. C.; Dao, X. D.; Nguyen, D. V.; Luu, D. H.; Bui, T. M. H.; Le, T. H.; Nguyen, H. T.; Le, T.N.; Hosaka, T.; & Nguyen, T. T. T. (2023). Insulin signaling and its application.

Frontiers in Endocrinology, 14, 1226655. https://doi.org/10.3389/fendo.2023.1226655

8. Le Roith, D.; & Zick, Y. (2001). Recent Advances in Our Understanding of Insulin Action and Insulin Resistance. Diabetes Care, 24(3), 588–597. https://doi.org/10.2337/diacare.24.3.588
9. Ma, J.; Dong, Y.; Liu, J.; Gao, S.; & Quan, J. (2025). The role of GRB2 in diabetes, diabetes complications and related disorders. Diabetes, Obesity and Metabolism, 27(1), 23–34. https://doi.org/10.1111/dom.16015.
10. AbdlWhab, H. M.; Al-Saffar, A.; Mahdi, O. A.; & Alameri, R. B. (2024). The impact of insulin resistance and glycaemic control on insulin-like growth factor-1 in patients with type 2 diabetes: A cross- sectional study. Clinical Diabetes and Endocrinology, 10(1), 36. https://doi.org/10.1186/s40842-024- 00202-8.
11. Zhang, S.; Wang, Q.; Ding, X.; Wang, T.; Mu, X.; & Chen, Z. (2016). Association of polymorphisms in PATE1 gene with idiopathic asthenozoospermia in Sichuan, China. Journal of Reproductive Immunology, 118, 54–60. https://doi.org/10.1016/j.jri.2016.08.007
12. Sheet, A. S.; Al-Shiti, A. Y.; Dawood, I. T.; Rasol, A. H.; Hasouni, A. M.; & Faisal, R. M. (2024). Phylogeny, susceptibility and virulence determinants of Morganella morganii isolated from patients with urinary tract infections in Mosul, Iraq. Regulatory Mechanisms in Biosystems, 15(4), 957-961.
13. Wang, S.; Sun, H.; Huang, R.; Wang, P.; Cai, R.; Xia, W.; Sun, J.; & Tian, S. (2017). Glycogen synthase kinase-3β (GSK-3β) rs334558 polymorphism is not associated with mild cognitive impairment in Chinese Han type 2 diabetic patients.
14. Raufi, S.; & Abad, S. Z. B. (2020). Molecular study of organic base changes in the IRS gene associated with gestational diabetes.
15. George, D.; & Mallery, P. (2019). IBM SPSS Statistics 26 Step by Step: A Simple Guide and Reference (6th ed.). Routledge. https://doi.org/10.4324/9780429056765
16. Dong, Y.; Liu, J.; Ma, J.; Quan, J.; Bao, Y.; & Cui, Y. (2022). The possible correlation between serum GRB2 levels and carotid atherosclerosis in patients with type 2 diabetes mellitus. Frontiers in Endocrinology, 13, 963191. https://doi.org/10.3389/fendo.2022.963191.
17. Liu, X.; Liu, M.; Zhang, J.; Bai, X.; Ramos, F.; Van Remmen, H.; Richardson, A.; Liu, F.-Y.; Dong,L. Q.; & Liu, F. (2009). Downregulation of Grb2 contributes to the insulin-sensitizing effect of calorie restriction. American Journal of Physiology-Endocrinology and Metabolism, 296(5), E1067–E1075. https://doi.org/10.1152/ajpendo.90714.2008
18. Bastos, C. M. C., Da Silva Machado, L. M., Crispim, D., Canani, L. H., & Dos Santos, K. G. (2024). Association of the rs9896052 Polymorphism Upstream of GRB2 with Proliferative Diabetic Retinopathy in Patients with Less than 10 Years of Diabetes. International Journal of Molecular Sciences, 25(19),
19. Rosen, N.; Mukherjee, R.; Pancholi, P.; Sharma, M.; Solomon, H.; Timaul, M.; Thant, C.; McGriskin, R.; Hayatt, O.; Markov, V.; D'Allara, J.; Bekker, S.; Candelier, J.; Carrasco, S.; De Stanchina, E.; & Vanaja, K. (2024). Diet induced insulin resistance is due to induction of PTEN expression. In Review. https://doi.org/10.21203/rs.3.rs-4021885/v1
20. Cook, J. R., Bedeir, N., Sone, Z. D., Wattacheril, J., Ginsberg, H. N., & Laferrère, B. (2024). Single Dose of Phosphatidylinositol 3-Kinase Inhibitor Alpelisib Induces Insulin Resistance in Healthy Adults: A Randomized Feasibility Study. Diabetes, 73(12), 2003–2008. https://doi.org/10.2337/db24-040210232. https://doi.org/10.3390/ijms251910232
21. Dong, L.; Hou, X.; Liu, F.; Tao, H.; Zhang, Y.; Zhao, H.; & Song, G. (2019). Regulation of insulin resistance by targeting the insulin-like growth factor 1 receptor with microRNA-122-5p in hepatic cells. Cell Biology International, 43(5), 553–564. https://doi.org/10.1002/cbin.11129.
22. Van Gerwen, J.; Shun-Shion, A. S.; & Fazakerley, D. J. (2023). Insulin signalling and GLUT4 trafficking in insulin resistance. Biochemical Society Transactions, 51(3), 1057–1069. https://doi.org/10.1042/bst20221066.
23. Herman, R.; Kravos, N. A.; Jensterle, M.; Janež, A.; & Dolžan, V. (2022). Metformin and Insulin Resistance: A Review of the Underlying Mechanisms behind Changes in GLUT4-Mediated Glucose Transport. International Journal of Molecular Sciences, 23(3),

1264.https://doi.org/10.3390/ijms23031264.

24. Gao, L.; Chen, J., Gao, J; Wang, H.; & Xiong, W. (2017). Super-resolution microscopy reveals the insulin-resistance-regulated reorganization of GLUT4 on plasma membranes. Journal of Cell Science, 130(2), 396–405. https://doi.org/10.1242/jcs.192450
25. Khorami, S. A. H.; Mutalib, M. S. A.; Shiraz, M. F.; Abdullah, J. A.; Rejali, Z.; Ali, R. M.; & Khaza'ai,H. (2020). Gene Expression of GSK3 in Type II Diabetics Compared to Non-Diabetics (ex vivo). The Open Diabetes Journal, 10(1), 30–37. https://doi.org/10.2174/1876524602010010030.
26. Arneth, B.; Arneth, R.; & Shams, M. (2019). Metabolomics of Type 1 and Type 2 Diabetes. International Journal of Molecular Sciences, 20(10), 2467. https://doi.org/10.3390/ijms20102467.
27. Delangre, E.; Liu, J.; Tolu, S., Maouche, K.; Armanet, M.; Cattan, P.; Pommier, G.; Bailbé, D.; & Movassat, J. (2021). Underlying mechanisms of glucocorticoid-induced β-cell death and dysfunction: A new role for glycogen synthase kinase 3. Cell Death & Disease, 12(12), 1136. https://doi.org/10.1038/s41419-021-04419-8
28. Nguyen, L. L.; Kriketos, A. D.; Hancock, D.; Caterson, I. D.; & Denyer, G. (2006). Insulin resistance does not influence gene expression in skeletal muscle. Journal of Biochemistry and Molecular Biology, 39(4), 457–463. https://doi.org/10.5483/BMBREP.2006.39.4.457.
29. Yousef, A.; Behiry, E.; Abd Allah, W.; Hussien, A.; Abdelmoneam, A.; Imam, M.; & Hikal, D. (2018). IRS-1 genetic polymorphism (r.2963G>A) in type 2 diabetes mellitus patients associated with insulin resistance. The Application of Clinical Genetics, Volume 11, 99–106. https://doi.org/10.2147/TACG.S171096.
30. Bhattacharjee, A.; Pranto, S. M. A. M.; Ahammad, I.; Chowdhury, Z. M.; Juliana, F. M.; Das, K. C.; Keya, C. A.; & Salimullah, M. (2023). High risk genetic variants of human insulin receptor substrate 1(IRS1) infer structural instability and functional interference. Journal of Biomolecular Structure and Dynamics, 41(24), 15150–15164. https://doi.org/10.1080/07391102.2023.2187232