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Identification of Novel Target Genes Linked to Type 2 Diabetes: An in Silico Approach

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KEYWORDS

Diabetic mellitus, Differentially expressed genes, Protein-protein interaction, KEGG Pathway, Gene Ontology.

ABSTRACT:

Introduction: Type 2 diabetes is a progressive metabolic disorder that causes morbidity and mortality all around the world. Though several drugs are available to manage diabetes, none of them effectively lower diabetes without causing adverse effects. As a result, finding novel genes associated with diabetes can lead to the development of novel approaches to therapy.

Objectives: The purpose of this study is to find potential genes linked to type 2 diabetes using in silico methods.

Methods: The Gene Expression Omnibus (GEO) analysis approach was employed to find new genes in the current work. GSE12634's expression was taken from the GEO database. The DEGs were identified using the GEO2R on the web application. Both gene ontology (GO) word enrichment analysis and Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway analysis were performed. The PPI network for differentially expressed genes (DEGs) was established by using the Cytoscape tool to identify significant functional pathways and gene candidates.

Results: GEO2R was used to filter a total of 250 DEGs, of which 65 were upregulated and 185 were downregulated. According to GO analysis, DEGs had significantly higher levels of extracellular matrix organization, extracellular structural organization, extracellular matrix-containing collagen, contractile fiber, and membrane raft. As for the KEGG pathway analysis reveals that DEGs were considerably abundant in the pathways related to diabetic complications such as AGE-RAGE, P13K-AKT, Tyrosine metabolism, Glycolysis/Gluconeogenesis, Glycosaminoglycan degradation, Pyruvate metabolism, and RAPI signaling. Six gene candidates were discovered (MMP2, CXCL2, CDH2, GSN, PPARG, DPP4, and SPP1) based on protein-protein interaction (PPI) network research.

Conclusions: In conclusion, our findings suggest that the genes CIR, CXCL12, CD44, SGCA, AGTR1, and TPM1 may be targets for diabetes condition, as they provide a number of bioinformatics investigations of gene pathways.

1. Introduction

After cancer and heart disease, type 2 diabetes mellitus (T2DM) is now the third most common chronic non-infectious disease affecting individuals worldwide. Approximately 425 million people worldwide currently have diabetes, with T2DM 2 accounting for the majority of cases [1]. According to the International Diabetes Federation, 629 million people worldwide will have diabetes by 2045, with Type 2 diabetes accounting for over 90% of cases. Type 2 diabetes is characterized by insulin resistance and pancreatic β-cell dysfunction [2]. Blood glucose irregularities are known to be the origin of type 2 diabetes, a chronic condition. This illness affects a bigger proportion of the global population and kills quietly. To combat this condition, it has been said that new biological candidates, potential target

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hypoglycemic medicines, and viable therapy approaches are required. Diabetes mellitus (DM) is a chronic metabolic disorder characterized by high blood glucose levels due to insulin resistance, inadequate insulin production, or both. Despite the fact that sub chronic immune-inflammatory pathways are implicated in the disease's pathogenesis, peripheral insulin resistance, which is commonly a by-product of obesity, appears to be the key component leading to the development of T2D [3]. Hyperglycemia is the major symptom of diabetes, a metabolic disease [4]. Type 2 diabetes mellitus is caused by insulin resistance as well as irregular insulin secretion [5]. People with type 2 diabetes mellitus have microvascular problems such as retinopathy and neuropathy, as well as macrovascular concerns such as cardiovascular comorbidities, which contribute to the development of insulin resistance (metabolic syndrome) and hyperglycemia [6]. Diabetes patients are at a two- to four-fold increased risk of cardiovascular disease, and endothelial cell dysfunction plays an important role in the development and progression of vascular issues [7,8]. Diabetes is a heterogeneous condition with multiple genetic pathways, according to current research. Although there appears to be a connection between a variety of biological systems and the development of type 2 diabetes, our present understanding of the intricacies of these systems and how they interact has delayed the development of viable treatments for the illness [9].

Gene expression analysis utilizing microarray technology is a potent and high-throughput research approach. Using gene expression profiling, numerous studies have discovered that hundreds of differentially expressed genes (DEGs) are associated with unique biological processes, signaling networks, and molecular functions. These pathways influence the onset and progression of diseases and may be used as a molecular target and diagnostic marker in T2DM [10]. The current study sought to identify possible genes connected to type 2 diabetes utilizing in silico approaches. The data generated can be used to develop new therapeutic strategies for treating T2DM.

2. **Methods**

2.1. Microarray Data sets:

The data set based on the GSE12643 Illumina Next Seq 500 (Homo sapiens) was retrieved from GEO (https://www.ncbi.nlm.nih.gov/geo/geo2r/?acc=GSE12643) [11]. Total of 6 samples were analysed, 3 of diabetic samples, and 3 controls (non diabetic).

2.2. DEG analysis:

GEO2R can be used to discover genes that differ in expression across different study conditions and to compare two or more sample groups. DEGs were identified in the dataset GSE12634 by linking the gene expression patterns of diabetic individuals. This analysis was conducted using R programming and GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/?acc

=GSE12634). The cut-off criteria were $P<0.05$ and log (fold change) ≥1. The DEGs were projected on a heat map with the R Studio 4.3.1 programming tool. (x86_64-w64-mingw32/x64). The R Foundation's Statistical Computing Platform [12].

2.3. Functional and pathway enrichment analysis

Pathway enrichment studies use statistical procedures to organize the results of pathways by frequency in the gene list and represent the enrichment as a probability value known as the *p* value [13]. The Kyoto Encyclopaedia of Genes and Genomes (KEGG), Gene Ontology (GO), is to perform enrichment analysis on gene sets. An enrichment analysis will determine which GO terms are overrepresented utilizing annotations for specific set of genes that are up-regulated under certain conditions. The DEGs were enriched using the Database of Annotation Visualization and Integrated Discovery (DAVID 6.8; https://david.ncifcrf.gov/) [14, 15]. The GO categories were biological process (BP), molecular function (MF), and cellular component (CC). A statistically significant difference was classified as $P < 0.05$ [16].

2.4 PPI (Protein-Protein Interaction) analysis:

String Database (https://string-db.org/) provides predicted and verified protein interactions that are used to create PPI networks [17, 18]. The combined study used the following data: The network has 100 nodes, 258 edges, an average node degree of 5.16, an average local clustering coefficient of 0.45, 92 predicted edges, and a PPI enrichment p-value of less than 1.0e-16. To discover hub genes and censorious gene modules, the screened PPI network was loaded into Cytoscape 3.2.1 (http://www.cytoscape.org/). Hub nodes have ≥5 times

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the median number of links with other nodes, while significant nodes have ≥2 times the median number of associates [19, 20].

3. Results

3.1. Identification of DEGs:

Based on the previously mentioned threshold log (fold change) ≥1 and P<0.05 a total of 250 DEGs including 65 upregulated DEGs and 185 downregulated DEGs were filtered with GEO2R (Figure: 1. a, b).

3.2. GO Analysis and

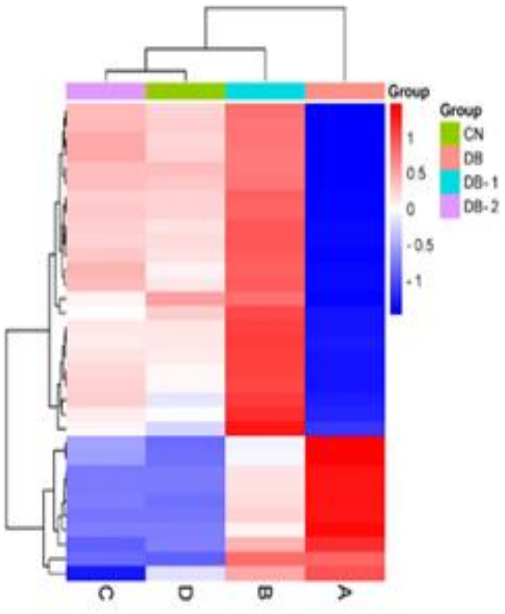
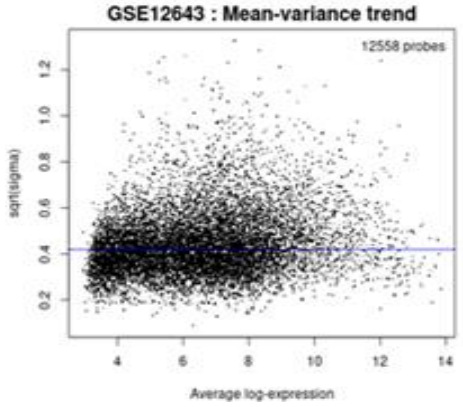


Figure.1 a) Heat-map of the 50 top downregulated and upregulated gens.



(b) DEGs in diabetes which represent control, and diabetes (P<0.05).

3.2. KEGG Pathway

In the GO category BP, upregulated genes were mostly enriched, mainly associated with extracellular matrix organization, extracellular structure organization and regulation of endopeptidase activity whereas downregulated genes were mainly associated with extracellular matrix organization, extracellular structure organization, regeneration, post-translational protein modification and regulation of endopeptidase activity (Table 1). In the GO category CC, the gene upregulated were mostly associated collagen-containing extracellular matrix, contractile fibre, external side of plasma membrane and membrane raft. Similarly, downregulated genes were mostly associated in collagen-containing extracellular matrix, contractile fibre, external side of plasma membrane, membrane raft, endoplasmic reticulum lumen and secretory granule lumen. In the GO category MF, upregulated genes were mostly associated with in peptide binding, amide binding and phospholipid binding and for down regulated genes peptide binding, amide binding, phospholipid binding, signalling receptor activator activity and receptor ligand activity.

Table 1: GO Analysis of down and up regulated gene in diabetes

BP					
		UPREGULATED GENES			
SL NO	ID	DESCRIPTION	P VALUE	GENES	COUNT
1	GO:0030198	extracellular matrix	1.06916E-07	ITGA6, PDGFA, SPP1, IL6,	7

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		organization		BGN, ITGA7, TNFRSF11B	
2	GO:0043062	extracellular structure organization	1.11209E-07	ITGA6, PDGFA, SPP1, IL6, BGN, ITGA7, TNFRSF11B	7
3	GO:0052548	Regulation of endopeptidase activity	3.65058E-06	VEGFA	1

DOWN REGULATED GENES

SL NO	ID	DESCRIPTION	P VALUE	GENES	COUNT
1	GO:0030198	extracellular matrix organization	1.06916E-07	FBLN1, KAZALD1, SLC39A8, RAMP2, MMP2, CTSK, COL9A3, CD44, TNC, LAMB1, ITGB2, DPP4	12
2	GO:0043062	extracellular structure organization	1.11209E-07	FBLN1, KAZALD1, SLC39A8, RAMP2, MMP2, CTSK, COL9A3, CD44, TNC, LAMB1, ITGB2, DPP4	12
3	GO:0031099	regeneration	2.86073E-06	CXCL12, CPQ, TYMS, GSN, LPIN1, SGCA, PCNA, PPARG	8
4	GO:0043687	post-translational protein modification	0.000236003	FSTL3, PSMB8, MFGE8, PENK, APLP2	5
5	GO:0052548	regulation of endopeptidase activity	0.003662365	SERPING1, SPOCK1, RARRES1, CRYAB, PSMB8	5

CC

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UPREGULATED GENE					
SI.NO	ID	Description	P value	Genes	Count
1	GO:0062023	collagen-containing extracellular matrix	2.56982E-07	TGM2, CDH2	2
2	GO:0043292	contractile fibre	0.000303772	PDLIM3, ANKRD1, ACTA2, TNN1, TPM1	5
3	GO:0009897	external side of plasma membrane	0.000714803	SLC7A5, HLA-F	2
4	GO:0045121	membrane raft	0.001041887	SMURF2, SLC25A5	2

DOWNREGULATED GENE					
SI.NO	ID	Description	P Value	Gene	Count
1	GO:0062023	collagen-containing extracellular matrix	2.56982E-07	SRPX, SOD3, CLU, SFRP1, ANGPTL2	5
2	GO:0043292	contractile fiber	0.000303772	ATP2B4, SVIL, HABP4	3
3	GO:0009897	external side of plasma membrane	0.000714803	FCGRT, IL1R1, CXCL12, CRLF1, ADA	5
4	GO:0045121	membrane raft	0.001041887	STOM, EZR, MME, SGCA	4
5	GO:0005788	endoplasmic reticulum lumen	1.62211E-06	CNPY3, TOR1A, F10	3
6	GO:0034774	secretory granule lumen	1.32418E-05	CHI3L1, CLU, CFD, GM2A, GUSB, CTSA, SDCBP, PROS1, AGA	9

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MF					
UPREGULATED GENES					
SL NO	ID	DESCRIPTION	P VALUE	GENE	COUNT
1	GO:0042277	peptide binding	0.000255228	SLC7A5, NUP58, PICALM	3
2	GO:0033218	amide binding	0.00050827	SLC7A5, NUP58, PICALM	3
3	GO:0005543	phospholipid binding	0.000843011	ZFYVE9, PRKCI	2

		DOWNREGULATED GENES			
SL NO	ID	DESCRIPTION	P VALUE	GENES	COUNT
1	GO:0042277	peptide binding	0.000255228	CLU, ITGB2	2
2	GO:0033218	amide binding	0.00050827	CLU, ITGB2	2
3	GO:0005543	phospholipid binding	0.000843011	APOC1, SNX1 ZCCHC14	3
4	GO:0030546	signalling receptor activator activity	0.028186275	FGF7	1
5	GO:0048018	receptor ligand activity	0.026428143	FGF7	1

Integrin Subunit Alpha 6: ITGA6 **,**PDGFA :Platelet Derived Growth Factor Subunit A,SPP1: Secreted Phosphoprotein 1,IL6:Interleukin 6 ,BGN: Biglycan, ITGA7: Integrin Subunit Alpha 7, TNFRSF11B: TNF Receptor Superfamily Member 11b, VEGFA: Vascular Endothelial Growth Factor A, FBLN1: Fibulin 1, KAZALD1: Kazal Type Serine Peptidase Inhibitor Domain 1, SLC39A8: Solute Carrier Family 39 Member 8, RAMP2: Receptor Activity Modifying Protein 2, MMP2: Matrix Metallopeptidase 2, CTSK: Cathepsin K, COL9A3: Collagen Type IX Alpha 3 Chain, CD44: CD44 Molecule (Indian Blood Group), TNC: Tenascin C, LAMB1: Laminin Subunit Beta, ITGB2: Integrin Subunit Beta 2, DPP4: Dipeptidyl Peptidase 4, CXCL12: C-X-C Motif Chemokine Ligand 12, CPQ: Carboxypeptidase Q, TYMS- Thymidylate Synthetase, GSN: Gelsolin, LPIN1: Lipin 1, SGCA: Sarcoglycan Alpha, PCNA: Proliferating Cell Nuclear Antigen , PPARG: Peroxisome Proliferator Activated Receptor Gamma , FSTL3: Follistatin Like 3, PSMB8: Proteasome 20S Subunit Beta 8, MFGE8: Milk Fat Globule EGF And Factor V/VIII Domain Containing, PENK: Proenkephalin, APLP2: Amyloid Beta Precursor Like Protein 2, SERPING1: Serpin Family G Member 1, SPOCK1: SPARC (Osteonectin), Cwcv And Kazal Like Domains Proteoglycan 1, RARRESL: Retinoic Acid Receptor Responder 1, CRYAB: Crystallin Alpha B, PSMB8: Proteasome 20S Subunit Beta 8, TGM2: Transglutaminase 2, CDH2: Cadherin 2, PDLIM3: PDZ And LIM Domain 3, ANKRD1: Ankyrin Repeat Domain 1, ACTA2 : Actin Alpha 2, Smooth Muscle, TPM1: Tropomyosin 1

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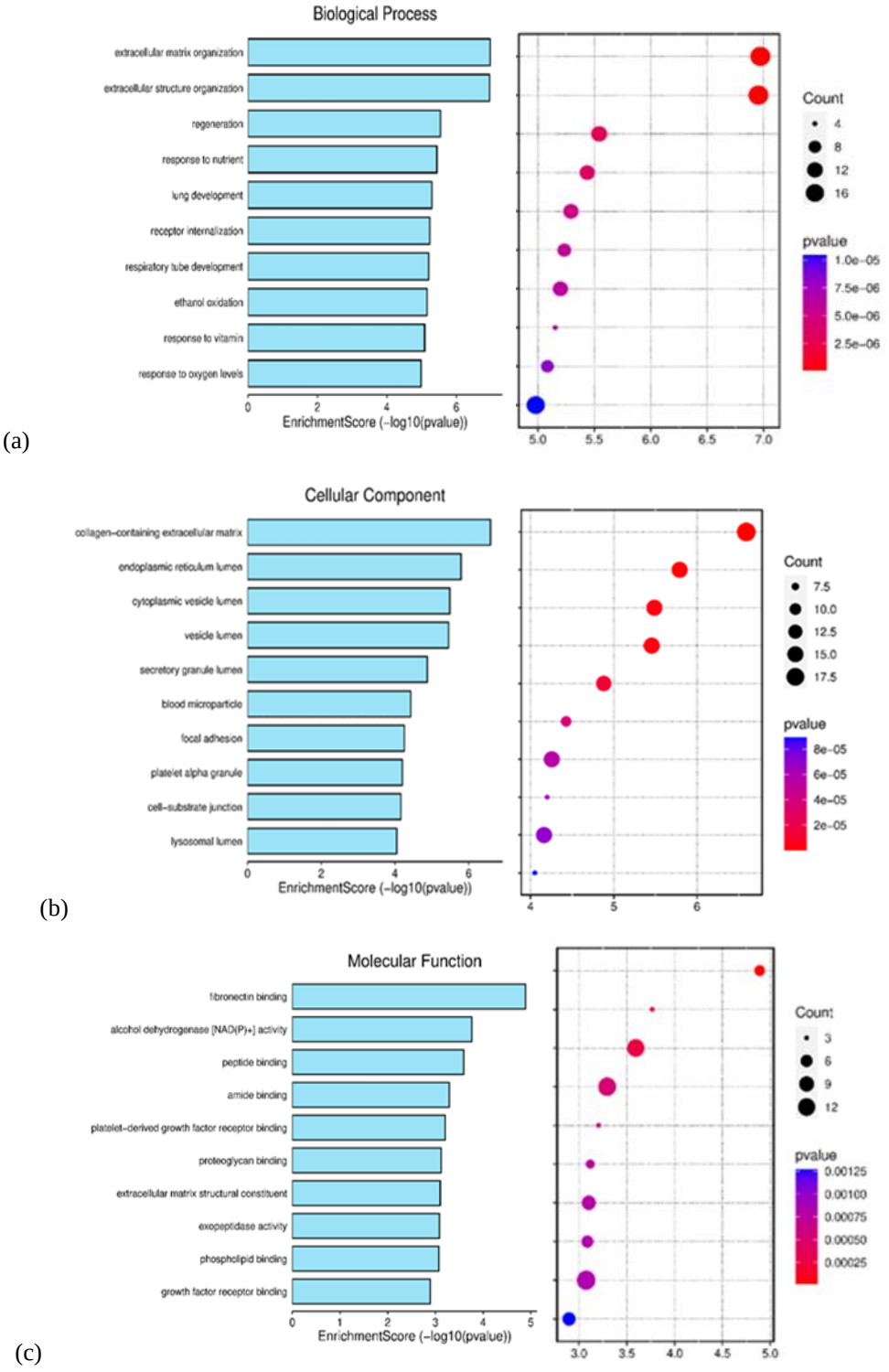

Figure 2: Enriched Gene Ontology analysis of differential expressed gene. 2a) BP: Biological process, 2b) CC: Cellular component, 2c) MF: Molecular function

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The pathway analysis conducted by KEGG showed that DEGs were significant association with the Glycolysis/ Gluconeogenesis, Tyrosine metabolism, Glycosaminoglycan degradation, Pyruvate metabolism, RAPI signalling pathway, Calcium signalling pathway, P13K- AKT signalling pathway, AGE-RAGE signalling pathway in diabetic complications.

Table 2: Analysis of up- and downregulated genes in diabetes is provided in the Kyoto Encyclopaedia pathway of Genes and Genomes (P<0.05)

KEGG PATHWAY					
UPREGULATED GENES					
SL NO	ID	DESCRIPTION	P VALUE	GENES	COUNT
1	hsa04810	Regulation of actin cytoskeleton	0.000111388	ITGA6, PDGFA, RRAS2, ITGA7	4
2	hsa04142	Lysosome	0.000628063	SPP1	1
3	hsa05410	Hypertrophic cardiomyopathy	0.00187436	TPM1	1
4	hsa00010	Glycolysis / Gluconeogenesis	0.002756358	BPGM	1
5	hsa04614	Renin-angiotensin system	0.004236767	AGTR1	1
6	hsa04936	Alcoholic liver disease	0.004431537	IL6	1

DOWN REGULATED GENES					
SL NO	ID	DESCRIPTION	P VALUE	GENES	COUNT
1	hsa04610	Complement and coagulation cascades	3.58778E-08	C1R, C1S, CLU, CFB, CFD, PROCR, F10, BDKRB2, ITGB2, PROS1	10
2	hsa04810	Regulation of actin cytoskeleton	0.000111388	CXCL12, LPAR1, EZR, GSN, BAIAP2, FGF7	6

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3	hsa04512	ECM-receptor interaction	0.000268434	COL9A3, CD44, TNC, LAMB1	4
4	hsa04142	Lysosome	0.000628063	CD68, CTSF, GM2A, CTSK, GUSB, CTSA, HEXA, AGA	8
5	hsa05410	Hypertrophic cardiomyopathy	0.00187436	SGCA	1
6	hsa04614	Renin-angiotensin system	0.004236767	MME	1
7	hsa04936	Alcoholic liver disease	0.004431537	ADH1C, ADH1A, ADH1B, LPIN1, PRKAB2, ALDH2	6
8	hsa00620	Pyruvate metabolism	0.004603549	ADH1C, ADH1B, ADH1A, ALDH2	4

ITGA6: Integrin Subunit Alpha 6, PDGFA: Platelet Derived Growth Factor Subunit A, RRAS2: RAS Related 2, ITGA7: Integrin Subunit Alpha 7, SPP1: Secreted Phosphoprotein 1, TPM1: Tropomyosin 1, BPGM: Bisphosphoglycerate Mutase, AGTR1: Angiotensin II Receptor Type 1, IL6: Interleukin 6, C1R: Complement C1r, C1S: Complement C1s, CLU: Clusterin, CFB: Complement Factor B, CFD: Complement Factor D, PROCR: Protein C Receptor, F10: Coagulation Factor 10, BDKRB2: Bradykinin Receptor B2, ITGB2: Integrin Subunit Beta 2, PROS1: Protein S, CXCL12: C-X-C Motif Chemokine Ligand, LPAR1: Lysophosphatidic Acid Receptor 1, EZR: Ezrin, GSN: Gelsolin, BAIAP2: BAR/IMD Domain Containing adaptor Protein 2, FGF7: Fibroblast Growth Factor 7, COL9A3: Collagen Type IX Alpha 3 Chain, CD44: CD44 Molecule (IN BLOOD GROUP), TNC: Tenascin C, LAMB1: Lminin Subunit Beta 1, CD68: CD68 Molecule, CTSF: Cathepsin F, GM2A: Ganglioside GM2 Activator, GUSB: Glucuronidase Beta, CTSA: Cathepsin A, HEXA: Hexosaminidase Subunit Alpha, AGA: Aspartylglucosaminidase, SGCA: Sarcoglycan Alpha, MME: Membrane Metalloendopeptidases, ADH1C: Alcohol Dehydrogenase 1C (Class I), Gamma Polypeptide, ADH1A: Alcohol Dehydrogenase 1C (Class I), Alpha Polypeptide, ADH1B: Alcohol Dehydrogenase 1C (Class I), Beta Polypeptide, LPIN1: Lipin 1, PRKAB2: Protein Kinase AMP- Activated Non- Catalytic Subunit Beta 2, ALDH2: Aldehyde Dehydrogenase 2 Family Member.

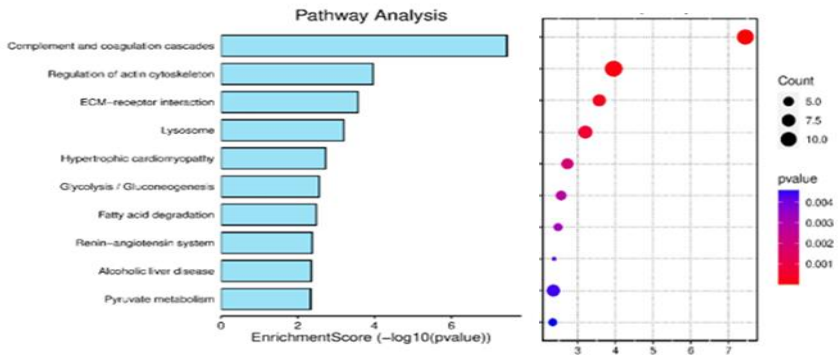

Figure.3: The pathway of KEEG analysis of upregulated and down regulation genes in diabetes (P<0.05)

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3.3 PPI Analysis:

The PPI network analysis results as available a total of 25 genes were considered as number for hub genes (Table 3) (Figure 5). Finally has presented in (Table 4), 7 hub genes involved in this - C-X-C Motif Chemokine Ligand 12 (CXCL12) with number of nodes 11 and number of edges 55, Matrix Metallopeptidase 2 (MMP2) with number of nodes 11 and number of edges 49, Cadherin 2 (CDH2) number of nodes 11 and number of edges 40, Gelsolin (GSN) number of nodes 11 and number of edges 47, Peroxisome Proliferator Activated Receptor Gamma (PPARG) number of nodes 11 and number of edges 49, Dipeptidyl Peptidase 4 (DPP4) number of nodes 11 and number of edges 26 and Secreted Phosphoprotein 1 (SPP1) number of nodes 11 and number of edges 39.

Table 3: The hub node gene analysis of differentially expressed genes.

Hub node 1	Hub node 2	Node 1 accession	Node 2 accession	Score
ACTA2	MMP2	9606.ENSP00000224784	9606.ENSP00000219070	0.617
ACTA2	FBLN1	9606.ENSP00000224784	9606.ENSP00000331544	0.403
ACTA2	CXCL12	9606.ENSP00000224784	9606.ENSP00000379140	0.414
ACTA2	CDH2	9606.ENSP00000224784	9606.ENSP00000269141	0.415
ACTA2	GSN	9606.ENSP00000224784	9606.ENSP00000362924	0.425
ACTA2	CD68	9606.ENSP00000224784	9606.ENSP00000250092	0.482
AGTR1	PPARG	9606.ENSP00000398832	9606.ENSP00000287820	0.583
CLU	GSN	9606.ENSP00000315130	9606.ENSP00000362924	0.646
ADH1A	CDH2	9606.ENSP00000209668	9606.ENSP00000269141	0.639
ADH1A	ALDH2	9606.ENSP00000209668	9606.ENSP00000261733	0.975
ADH1A	ADH1C	9606.ENSP00000209668	9606.ENSP00000426083	0.983
ADH1B	ALDH2	9606.ENSP00000306606	9606.ENSP00000261733	0.995
ADH1B	ADH1C	9606.ENSP00000306606	9606.ENSP00000426083	0.986
ADH1C	ALDH2	9606.ENSP00000426083	9606.ENSP00000261733	0.989
AGTR1	MMP2	9606.ENSP00000398832	9606.ENSP00000219070	0.43
AGTR1	PPARG	9606.ENSP00000398832	9606.ENSP00000287820	0.583
BGN	SPP1	9606.ENSP00000327336	9606.ENSP00000378517	0.617
CD44	DPP4	9606.ENSP00000398632	9606.ENSP00000353731	0.643
CLU	PICALM	9606.ENSP00000315130	9606.ENSP00000377015	0.923
COL18A1	CXCL12	9606.ENSP00000352798	9606.ENSP00000379140	0.444
F10	MFGE8	9606.ENSP00000364709	9606.ENSP00000268150	0.439
AGTR1	BDKRB2	9606.ENSP00000398832	9606.ENSP00000450482	0.975

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APLP2	GSN	9606.ENSP00000497691	9606.ENSP00000362924	0.461
CD44	IL1R1	9606.ENSP00000398632	9606.ENSP00000386380	0.428

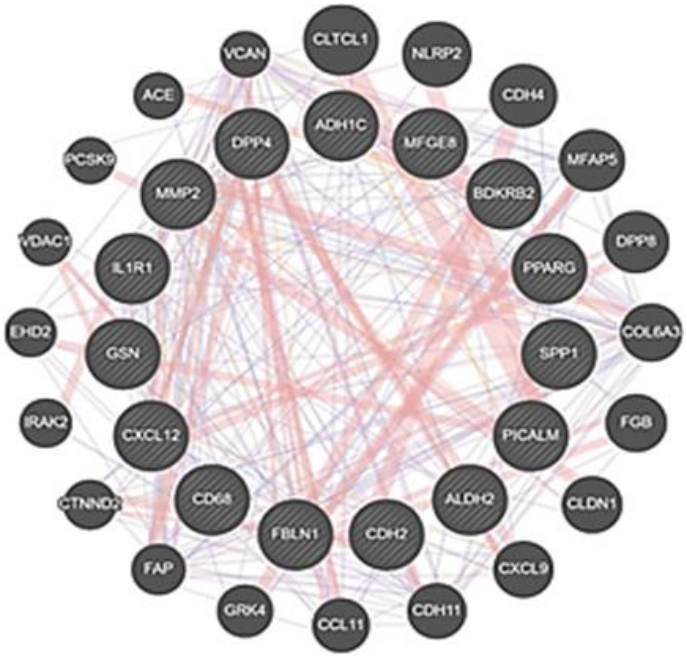

Figure 4: Genes with differentially expressed in core protein-protein interaction network with number of nodes:11, number of edges:8, average node degree:1.45, avg. local clustering coefficient:0.727, PPI enrichment p-value:0.000958.

Table 4: The number of genes selected from protein-protein interaction analysis.

Hub genes	Number of nodes	Number of edges	Average node degree	Average local clustering coefficient	Expected number of edges	PPI enrichment p- value
CXCL2	11	55	10	1	12	< 1.0e-16
MMP2	11	49	8.91	0.899	17	9.19e-11
CDH2	11	40	7.27	0.881	16	3.74e-0
GSN	11	47	8.55	0.902	12	1.22e-14
PPARG	11	49	8.91	0.923	19	4.58e-09
DPP4	11	26	4.73	0.805	16	0.0139
SPP1	11	39	7.09	0.868	15	1.5e-07

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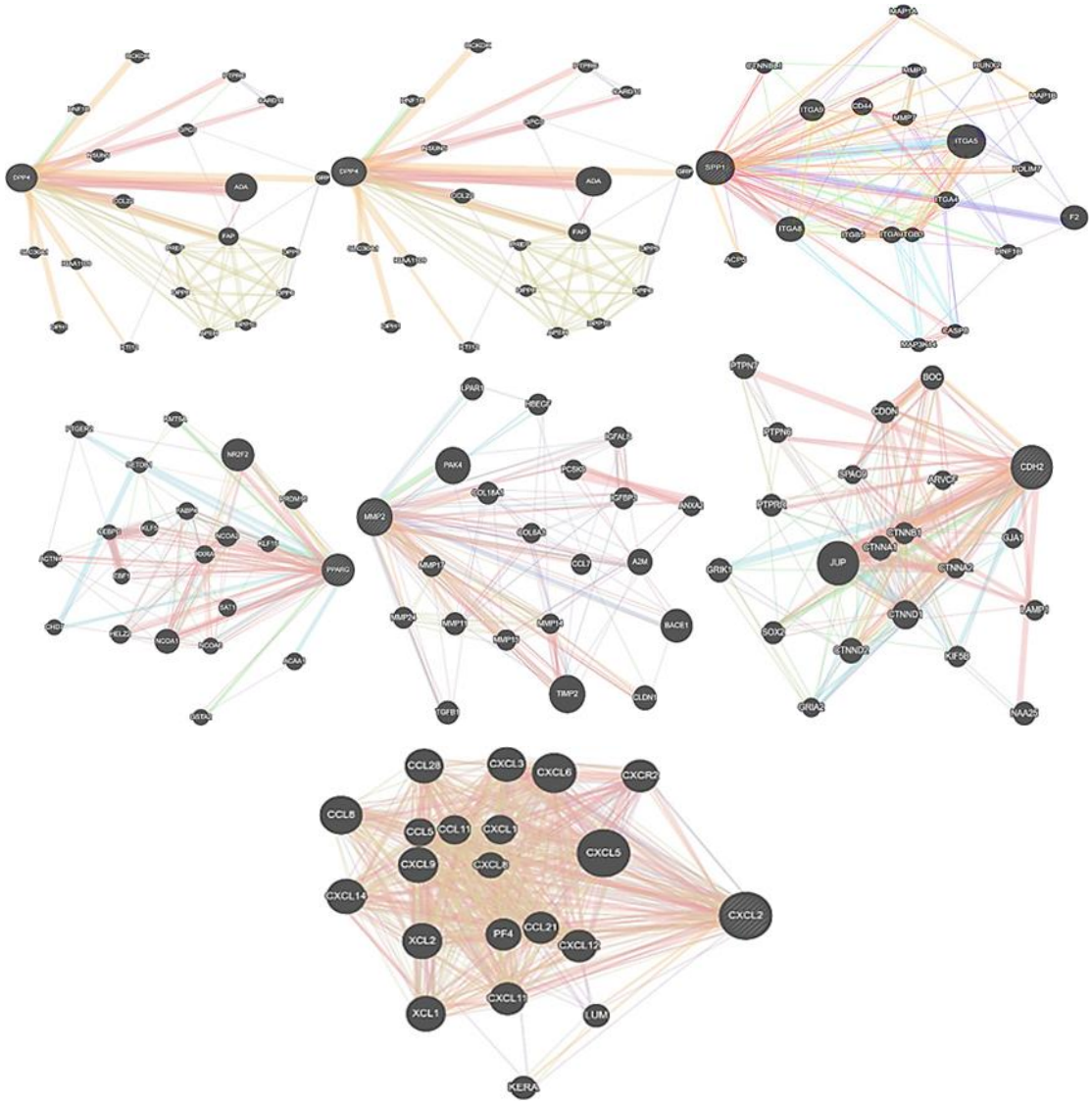

Figure 5: The PPI (protein-protein interaction) conducted for CXCL2, MMP2, CDH2, GSN, PPARG, DPP4 and SPP1 by STRING analysis.

4. Discussion

Diabetes mellitus (DM) is a long-term metabolic disorder characterized by continuously elevated blood sugar levels that is becoming increasingly frequent around the world [21]. Type 2 diabetes mellitus (T2DM) causes approximately 90% of all diabetes cases. Between 1980 and 2024, the prevalence of all types of diabetes almost doubled, rising from 4.7% to 8.5%. Diabetes affects approximately 463 million people worldwide in 2019, with the figure anticipated to rise by 25% in 2030 and 51% in 2045 [22]. In this study, we discovered 250 significant DEGs in both diabetes samples, including 185 downregulated and 65 upregulated genes. Next, we conducted a series of bioinformatic analyses to narrow down the genes and pathways associated with diabetes. DEGs were functionally annotated using GO word enrichment analysis and KEGG pathway analysis. According to the results of the GO term enrichment analysis, DEGs may play important roles in the organization of the extracellular matrix and extracellular structure in diabetes, the regulation of endopeptidase activity, regeneration, post-translational protein modification and the regulation of endopeptidase activity, contractile fiber, the membrane raft and external side of the plasma membrane, the extracellular matrix containing collagen, the membrane raft, the lumen

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Furthermore, by constructing the protein-protein interaction, 7 genes were found, which had a significant impact on diabetes. The genes chosen are CXCL2, MMP2, CDH2, GSN, PPARG, DPP4, and SPP1. The KEGG pathway analysis revealed that DEGs had a significant association with the Glycolysis/Gluconeogenesis, Glycosaminoglycan degradation, Pyruvate metabolism, RAPI signalling pathway, Calcium signalling pathway, P13K-AKT signalling pathway, Tyrosine metabolism, and AGE-

[26]. Diabetic nephropathy (DN) is the leading cause of end-stage kidney damage and one of the most common microvascular consequences of diabetes [27]. Patients with diabetes who also have renal involvement are three times more likely to die from cardiovascular disease than those with diabetes who do not show signs of renal failure. Diabetes and chronic renal disease both increase the risk of developing cardiovascular disease [28, 29]. Diabetes is a major global health concern that dramatically increases the risk of cardiovascular death. It is associated with a variety of physiological and pathological changes in the circulatory system. Endothelial dysfunction and hemostatic disorders may contribute to the increased risk of coronary artery disease (CAD), and the pathophysiology of a specific diabetic cardiomyopathy has been linked to micro angiopathy, myocardial fibroses, and abnormal myocardial metabolism. Heart failure in diabetics is typically caused by coronary artery disease (CAD). Furthermore, compared to the general population, RA patients are more prone to develop cardiovascular diseases (CVDs), with myocardial infarctions (MI) accounting for the vast majority of deaths. The concurrent existence of additional risk factors such as hyperlipidemia, hypertension, and diabetes mellitus (DM) may be the cause of this elevated risk [30].

5. **Conclusion**

In conclusion, our results revealed that pathway regulation network closely associated to diabetes was discovered through a series of bioinformatics analyses comparing DEGs between diabetes sample datasets and normal sample datasets. Our study sought to identify a few possible genes. Seven gene candidates were found using PPI network analysis: CXCL2, MMP2, CDH2, GSN, PPARG, DPP4, and SPP1. DEGs and KEGG pathway analysis suggested that CIR, CXCL12, CD44, RAGE signalling pathway in diabetic complications [23-24]. Diabetic nephropathy (DN) is one of the most common microvascular complications of diabetes mellitus and the leading cause of end-stage kidney damage. Diabetics with renal involvement are three times more likely to die from cardiovascular disease than diabetics without indications of renal failure [25]. Diabetes and chronic kidney disease are risk factors for cardiovascular disease [26]. Diabetes and chronic renal disease both increase the risk of cardiovascular disease

SGCA, AGTR1, and TPM1 have the potential to be employed in the diagnosis and treatment of diabetes. Furthermore, given the limitations of this study's clinical validation, additional experimental studies with techniques such as Western blot and qRT-PCR can validate the results obtained or anticipated by bioinformatics analysis.

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Authors' contributions

DKL performed experiments. VDR and VR designed the work. DKL, NS, MS, VU, SG, KG, VDR and VR wrote the paper. All authors read and approved the final manuscript.

Conflict of interests

None.

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