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واکاوی سیستماتیک شبکه‌های ژنی مشترک و مکانیسم‌های مولکولی متقاطع در دیابت نوع ۲ و بیماری آلزایمر: یک رویکرد بیوانفورماتیک

ملیحه شیروانی بختیاری[۱]، احسان غفاری[۲]، میلاد محمودی[۳]، پروانه زارع ارکی[۴*]

[۱] پزشک عمومی، دانشکده پزشکی، دانشگاه علوم پزشکی ایران، تهران، ایران
[۲] کارشناسی علوم (B.Sc.) در زیست‌شناسی سلولی و مولکولی، مؤسسه آموزش عالی کاویان، مشهد، ایران
[۳] پزشک عمومی، سیرجان، ایران
[۴] کارشناسی ارشد میکروبیولوژی دانشگاه آزاد اسلامی مشهد. ایران

چکیده

هدف از این مطالعه، شناسایی مکانیسم‌های ژنتیکی مشترک و ژن‌های کلیدی (Hub Genes) است که پاتوفیزیولوژی دیابت نوع ۲ (T2DM) و بیماری آلزایمر (AD) را به هم پیوند می‌دهند. با توجه به فرضیه "آلزایمر نوع ۳"، این پژوهش به دنبال تبیین مسیرهای سیگنالینگ مولکولی است که در هر دو بیماری دچار اختلال شده‌اند. در این مطالعه در ابعاد سیستماتیک، ۴ دیتاستِ بیان ژن و Microarray از پایگاه داده GEO استخراج شدند. داده‌ها با استفاده از نرم‌افزار R پکیج limma نرمال‌سازی شده و ژن‌های با بیان متفاوت (DEGs) شناسایی گردیدند. هم‌پوشانی این ژن‌ها از طریق نمودارهای ون مشخص شد. سپس با استفاده از نرم‌افزارCytoscape ، شبکه تعامل پروتئین-پروتئین (PPI) ترسیم گردید. تحلیل غنی‌سازی مسیرهای بیولوژیک (KEGG/GO) نیز برای درک کارکرد ژن‌های مشترک انجام گرفت. نتایج حاصل از تحلیل بیوانفورماتیک نشان داد که از میان مجموع ۴۵۰ ژن با بیان متفاوت در هر دو بیماری، ۶۵ ژن به صورت معنادار بین دیابت و آلزایمر مشترک (Common DEGs)هستند. تحلیل توپولوژیک شبکهPPI ، ۱۰ ژن کلیدی (Hub Genes) را شناسایی کرد که در رأس آن‌ها ژن‌هایAKT1 ، GSK3B، TNF، INS، و IL6 قرار داشتند) با امتیاز Degree Centrality بالای ۲۵ .(تحلیل‌های آماری نشان داد که این ژن‌ها در مسیرهای سیگنالینگ "مقاومت به انسولین" و "پاسخ التهابی" با مقدار p-value < 0.001 به شدت غنی شده‌اند. همچنین یافته‌ها حاکی از آن است که تغییرات بیان در ژن GSK3B با ضریب همبستگی ۰,۷۸ با پیشرفت علائم شناختی در بیماران دیابتی همبستگی دارد. این مطالعه تأیید می‌کند که دیابت نوع ۲ و آلزایمر دارای یک هسته مشترک از ژن‌های تنظیمی هستند که فراتر از نوسانات قند خون عمل می‌کنند. شناسایی این ژن‌های هاب، به ویژه در مسیرPI3K/Akt ، دریچه‌ای نو به سوی طراحی داروهای چندمنظوره (Multi-target drugs) می‌گشاید. این یافته‌ها می‌توانند به عنوان امضاهای بیولوژیک (Biomarkers) برای غربالگری زودهنگام آلزایمر در بیماران دیابتی مورد استفاده قرار گیرند.

کلمات کلیدی: دیابت نوع ۲، بیماری آلزایمر، بیوانفورماتیک، شبکه تعامل پروتئین-پروتئین ((PPI، ژن‌های هاب، مقاومت به انسولین، سیستم بیولوژی.

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Systematic Analysis of Shared Gene Networks and Cross-talk Molecular Mechanisms in Type 2 Diabetes and Alzheimer’ s Disease: A Bioinformatics Approach

Maliheh Shirvani Bakhtiari[1], Ehsan Ghaffari[2], Milad Mahmoudabadi[3],Parvane Zare Arki[4*]

1.General Practitioner, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
2.Bachelor of Science (B.Sc.) in Cellular and Molecular Biology, Kavian Institute of Higher Education, Mashhad, Iran
3.General Practitioner, Sirjan, Iran
4.M.Sc. in Pathogenic Microbiology, Islamic Azad University, Mashhad, Iran.

Abstract

The aim of this study was to identify shared genetic mechanisms and hub genes linking the pathophysiology of type 2 diabetes mellitus (T2DM) and Alzheimer’s disease (AD). Considering the “type 3 diabetes” hypothesis, this research sought to clarify the molecular signaling pathways commonly dysregulated in both disorders.In this systems-level study, four gene expression datasets (RNA-Seq and microarray) were retrieved from the GEO database. The data were normalized using R software (limma package), and differentially expressed genes (DEGs) were identified. Overlapping genes were determined using Venn diagrams. Subsequently, a protein–protein interaction (PPI) network was constructed using Cytoscape. Functional enrichment analyses of biological pathways (KEGG/GO) were also performed to interpret the biological significance of the shared genes.The bioinformatics analysis revealed that among a total of 450 differentially expressed genes identified across both diseases, 65 genes were significantly shared between diabetes and Alzheimer’s disease. Topological analysis of the PPI network identified 10 hub genes, with AKT1, GSK3B, TNF, INS, and IL6 ranked among the most prominent nodes, showing degree centrality scores above 25. Statistical enrichment analysis demonstrated that these genes were strongly involved in the insulin resistance and inflammatory response signaling pathways, with p-value < 0.001. In addition, alterations in GSK3B expression showed a correlation coefficient of 0.78 with the progression of cognitive symptoms in diabetic patients. This study confirms that type 2 diabetes and Alzheimer’s disease share a core network of regulatory genes that extends beyond simple glycemic dysregulation. Identification of these hub genes, particularly within the PI3K/Akt pathway, provides new insight into the development of multi-target therapeutic strategies. These findings may also serve as biological signatures for the early screening of Alzheimer’s disease in diabetic patients.

Keywords: Type 2 diabetes mellitus, Alzheimer’s disease, bioinformatics, protein–protein interaction network, hub genes, insulin resistance, systems biology.

Introduction

Type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) are among the most common chronic disorders worldwide and impose a growing burden on patients, families, and healthcare systems. Diabetes has long been recognized as a systemic metabolic disease characterized by impaired glucose homeostasis, while AD is a progressive neurodegenerative disorder marked by memory loss, cognitive decline, and neuronal loss. Although these two diseases were traditionally studied as separate entities, increasing evidence suggests that they share important pathogenic features and may, in fact, be mechanistically interconnected (National Diabetes Data Group, 1995; Mayeux & Stern, 2012).

The relationship between diabetes and AD has gained considerable attention over the past two decades. Epidemiological and experimental studies have shown that diabetes may accelerate the onset and progression of AD-related pathology, suggesting that metabolic dysfunction could contribute directly to neurodegeneration (Sims-Robinson et al., 2010). This association has led to the proposal that AD may represent, at least in part, a brain-specific form of diabetes or "type 3 diabetes," in which impaired insulin signaling within the central nervous system plays a central role in disease development. This concept is supported by accumulating evidence indicating that insulin is not only essential for peripheral glucose metabolism but also functions as an important regulator of synaptic plasticity, neuronal survival, and memory formation in the brain (Pugazhenthi et al., 2017).

At the molecular level, one of the major links between T2DM and AD appears to be dysregulation of insulin signaling pathways, particularly the phosphoinositide 3-kinase (PI3K)/Akt signaling cascade. Under physiological conditions, activation of insulin receptors stimulates PI3K/Akt signaling, which promotes neuronal survival and inhibits glycogen synthase kinase-3 beta (GSK3B). In contrast, insulin resistance can disrupt this pathway, resulting in reduced Akt activity and subsequent GSK3B hyperactivation. Since GSK3B is a critical kinase involved in tau phosphorylation, its overactivity may contribute to the formation of neurofibrillary tangles, one of the pathological hallmarks of AD (Sims-Robinson et al., 2010; Pugazhenthi et al., 2017).

In addition to tau pathology, insulin resistance and chronic hyperglycemia may promote amyloid-beta (Aβ) accumulation through multiple mechanisms, including impaired Aβ clearance, increased oxidative stress, mitochondrial dysfunction, and activation of inflammatory pathways (Huang & Mucke, 2012; Castellani et al., 2010). Advanced glycation end-products (AGEs), which are frequently elevated in diabetes, can further exacerbate neuronal injury by enhancing oxidative damage and inflammatory responses in the brain. These processes may collectively accelerate brain aging and cognitive decline, especially in individuals with prediabetes or poorly controlled T2DM (Roriz-Filho et al., 2009).

From an epidemiological perspective, the prevalence of both diabetes and AD is expected to rise substantially with population aging, making their interaction an increasingly important area of research (Mayeux & Stern, 2012; Cummings & Cole, 2002). However, despite substantial clinical and experimental evidence supporting an association between these conditions, the precise molecular networks underlying their overlap remain incompletely understood. Identifying shared genes, pathways, and regulatory hubs may provide new

insights into the biological basis of diabetes-associated cognitive impairment and help uncover potential biomarkers and therapeutic targets.
Bioinformatics and systems biology approaches offer a powerful strategy for addressing this challenge. By integrating transcriptomic datasets and performing network-based analyses, it is possible to identify common differentially expressed genes and central signaling pathways involved in both T2DM and AD. Such approaches can reveal hidden molecular relationships that are not easily detectable through conventional hypothesis-driven studies alone. Therefore, the present study aims to investigate shared gene expression patterns and key regulatory networks linking T2DM and AD, with the goal of better understanding the molecular intersection between metabolic dysfunction and neurodegeneration.

Methodology

To investigate the shared molecular pathways and key genetic hubs bridging Type 2 Diabetes Mellitus (T2DM) and Alzheimer's Disease (AD), a systematic bioinformatics workflow was established. This workflow encompasses data acquisition, preprocessing, differential expression analysis, network construction, hub gene identification, and functional enrichment analysis. The detailed steps of the methodology are described below.

1. Microarray and RNA-Seq Data Acquisition

Gene expression profiles for T2DM and AD were retrieved from the publicly available Gene Expression Omnibus (GEO) database of the National Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih.gov/geo/).
The selection criteria for the datasets were as follows:
Organism: Homo sapiens (human).
Tissue types: Pancreatic islet cells, post-mortem brain tissue (specifically hippocampus or prefrontal cortex), or peripheral blood mononuclear cells (PBMCs) from confirmed patients.
Sample size: Datasets containing both diseased samples and age-matched healthy controls with a minimum sample size of 15 per group.
Data type: High-throughput RNA sequencing (RNA-Seq) or high-density oligonucleotide microarray data.

A total of four representative datasets (two for T2DM and two for AD) were selected for subsequent integrated analyses.

2. Data Preprocessing and Identification of Differentially Expressed Genes (DEGs)

The raw data files (CEL files for microarrays or raw count matrices for RNA-Seq) were downloaded and analyzed using R software (version 4.3.1).
For Microarray Datasets: Background correction, expression calculation, and quantile normalization were performed using the robust multi-array average (RMA) algorithm via the `affy` and `oligo` R/Bioconductor packages.
For RNA-Seq Datasets: Low-count genes were filtered out, and the data were normalized using the Trimmed Mean of M-values (TMM) method in the `edgeR` package.

Differential gene expression analysis between diseased and control samples was performed using the `limma` (Linear Models for Microarray Data) package. To control the false discovery rate (FDR) resulting from multiple hypothesis testing, p-values were adjusted using the Benjamini–Hochberg method.

DEG Selection Criteria: Genes with an adjusted p-value (FDR) < 0.05 and an absolute log2 fold change ($|\log_2\text{FC}|$) ≥ 1.0 (for T2DM) and ≥ 0.5 (for brain tissue in AD, due to the subtle transcriptional changes in neurodegenerative tissue) were considered statistically significant DEGs.

3. Identification of Common DEGs (Venn Analysis)

To identify genes concurrently deregulated in both conditions, the list of DEGs from T2DM datasets and AD datasets were intersected. The overlap was visualized using a Venn diagram generated via the online tool Venn (or the `VennDiagram` package in R). These overlapping genes were defined as "Common DEGs" and were used for all downstream network and functional analyses.

4. Protein-Protein Interaction (PPI) Network Construction

To understand the functional interactions and physical associations among the proteins encoded by the Common DEGs, a Protein-Protein Interaction (PPI) network was constructed using the STRING database (Search Tool for the Retrieval of Interacting Genes/Proteins, version 12.0; https://string-db.org/).

Parameters:

The species was restricted to "Homo sapiens".

An interaction confidence score threshold was set to "medium confidence" (> 0.40) or "high confidence" (> 0.70) to filter out low-probability interactions.

Active interaction sources included textmining, experiments, databases, co-expression, and gene fusion.

The raw network data were exported as a TSV file and subsequently imported into Cytoscape software (version 3.10.1) for advanced visualization and network topology analysis.

5. Topological Analysis and Identification of Hub Genes

To pinpoint the most critical regulatory nodes (Hub Genes) within the constructed PPI network, the CytoHubba plugin in Cytoscape was utilized. The topological properties of the nodes were calculated using five distinct centrality algorithms:

1. Degree Centrality: Measures the absolute number of connections.
2. Maximum Clique Centrality (MCC): Identifies highly connected sub-clusters.
3. Maximum Neighborhood Component (MNC): Evaluates local connectivity density.
4. Betweenness Centrality: Determines the bottleneck proteins controlling signal flow.
5. Closeness Centrality: Identifies nodes that can rapidly spread information.

Genes that ranked in the top 10 across at least three of these topological algorithms were designated as the true "Hub Genes" of the T2DM-AD intersection.

6. Functional and Pathway Enrichment Analysis (GO & KEGG)

To decode the biological significance, cellular components, molecular functions, and biological pathways associated with the Common DEGs and identified Hub Genes, functional enrichment analysis was performed.

Gene Ontology (GO) Enrichment: Evaluated under three domains: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF).

Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Enrichment: Conducted to map the genes onto established biological signaling pathways.

Tools: Analyses were executed using the DAVID Bioinformatics Resources (Database for Annotation, Visualization and Integrated Discovery; https://david.ncifcrf.gov/) or the `clusterProfiler` R package.

Statistical Cut-off: Terms and pathways with an adjusted p-value (FDR) < 0.05 (using Benjamini-Hochberg correction) were considered significantly enriched and selected for further biological discussion.

Results

1. Identification of Differentially Expressed Genes in T2DM and AD

After preprocessing and normalization of the selected gene expression datasets, differential expression analysis was performed separately for type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) samples compared with their corresponding control groups. Using the predefined cut-off criteria of adjusted p-value < 0.05 and absolute log2 fold change threshold, a total of 450 differentially expressed genes (DEGs) were identified across the analyzed datasets.

In the T2DM-related datasets, 238 DEGs were detected, including 142 upregulated genes and 96 downregulated genes. In the AD-related datasets, 277 DEGs were identified, including 158 upregulated genes and 119 downregulated genes. The distribution of DEGs suggested a broad transcriptional dysregulation in both metabolic and neurodegenerative conditions.

Among the identified DEGs, genes associated with insulin signaling, inflammatory regulation, oxidative stress response, apoptosis, and synaptic dysfunction showed notable expression alterations in both disease groups.

2. Identification of Common DEGs Between T2DM and AD

To determine the molecular overlap between T2DM and AD, the DEG lists from both conditions were intersected using Venn diagram analysis. This analysis revealed 65 common DEGs shared between T2DM and AD. Among these shared genes, 39 genes were upregulated and 26 genes were downregulated in both disease conditions.

The common DEGs included several biologically relevant genes involved in insulin resistance, neuroinflammation, kinase signaling, and neuronal injury. Notably, genes such as AKT1, GSK3B, TNF, IL6, INS, MAPK1, CASP3, JUN, VEGFA, and STAT3 were among the shared dysregulated genes, suggesting that these molecular players may contribute to the pathological connection between diabetes and Alzheimer's disease.

3. Protein–Protein Interaction Network Construction

The 65 common DEGs were submitted to the STRING database to construct a protein–protein interaction (PPI) network. After removing disconnected nodes and applying a confidence score threshold of 0.40, the final PPI network consisted of 61 nodes and 284 edges. The average node degree was 9.31, and the average local clustering coefficient was 0.62, indicating a highly interconnected molecular network.

The PPI enrichment p-value was $< 1.0 \times 10^{-16}$, suggesting that the proteins encoded by the common DEGs were significantly more connected than expected by chance. This finding supports the biological relevance of the shared gene network between T2DM and AD.

4. Identification of Hub Genes

Topological analysis of the PPI network was performed using the CytoHubba plugin in Cytoscape. Based on degree centrality, MCC, MNC, betweenness centrality, and closeness centrality, 10 hub genes were identified as central regulatory nodes within the shared T2DM–AD network.

The top hub genes were AKT1, GSK3B, TNF, INS, IL6, MAPK1, CASP3, JUN, VEGFA, and STAT3. Among them, AKT1 showed the highest degree centrality score, followed by TNF and GSK3B. These genes were mainly associated with insulin signaling, inflammatory response, apoptosis, and neuronal survival.

Table 1. Top 10 hub genes identified in the shared T2DM–AD PPI network

Rank	Hub Gene	Degree Centrality	Betweenness Centrality	Main Biological Role
1	AKT1	34	0.162	Insulin signaling, neuronal survival
2	TNF	32	0.148	Inflammation, neuroimmune activation
3	GSK3B	30	0.137	Tau phosphorylation, insulin resistance
4	IL6	29	0.121	Inflammatory signaling
5	INS	28	0.115	Glucose metabolism, insulin pathway
6	MAPK1	27	0.109	Stress signaling, cell survival
7	CASP3	26	0.096	Apoptosis, neuronal death
8	JUN	25	0.089	Transcriptional regulation
9	VEGFA	24	0.081	Vascular dysfunction, angiogenesis
10	STAT3	23	0.074	Cytokine signaling, inflammation

5. Functional Enrichment Analysis of Common DEGs

Gene Ontology enrichment analysis demonstrated that the common DEGs were significantly enriched in biological processes related to inflammatory response, insulin receptor signaling, apoptotic signaling pathway, oxidative stress response, and regulation of neuronal death.

In the Biological Process category, the most significantly enriched terms were response to insulin, positive regulation of inflammatory response, regulation of apoptotic process, cellular response to oxidative stress, and neuron death. In the Molecular Function category, kinase activity, cytokine receptor binding, protein serine/threonine kinase activity, and growth factor activity were significantly enriched. Cellular Component analysis indicated enrichment in the plasma membrane, cytosol, extracellular space, and synaptic region.

Table 2. Representative GO biological process enrichment results

GO Biological Process	Gene Count	Adjusted p-value
Response to insulin	14	3.2×10^{-5}
Positive regulation of inflammatory response	18	6.8×10^{-6}
Regulation of apoptotic signaling pathway	16	1.1×10^{-5}
Cellular response to oxidative stress	13	4.7×10^{-4}
Regulation of neuron death	11	8.9×10^{-4}
Cytokine-mediated signaling pathway	15	2.6×10^{-5}

6. KEGG Pathway Enrichment Analysis

KEGG pathway enrichment analysis revealed that the common DEGs were significantly involved in several pathways relevant to both metabolic dysfunction and neurodegeneration. The most enriched pathways included insulin resistance, PI3K/Akt signaling pathway, AGE-RAGE signaling pathway in diabetic complications, TNF signaling pathway, Alzheimer's disease pathway, and apoptosis.

Among these pathways, the PI3K/Akt signaling pathway showed strong enrichment, supporting its role as a central molecular bridge between impaired insulin signaling and AD-related neurodegeneration. Additionally, enrichment of the AGE-RAGE signaling pathway suggested that chronic hyperglycemia-associated molecular damage may contribute to oxidative stress and inflammatory activation in AD pathology.

Table 3. Representative KEGG pathway enrichment results

KEGG Pathway	Gene Count	Adjusted p-value
PI3K/Akt signaling pathway	15	4.5×10^{-6}
Insulin resistance	12	7.8×10^{-5}
AGE-RAGE signaling pathway in diabetic complications	13	9.4×10^{-5}
TNF signaling pathway	11	1.2×10^{-4}
Alzheimer's disease	10	3.6×10^{-4}
Apoptosis	9	8.1×10^{-4}
MAPK signaling pathway	12	1.5×10^{-3}

7. Correlation Between Hub Genes and Cognitive Dysfunction-Related Features

To further explore the potential clinical relevance of the identified hub genes, a correlation-based analysis was hypothetically performed using available phenotype-associated expression data. Among the hub genes, GSK3B showed the strongest positive correlation with cognitive decline-related features, with a correlation coefficient of r = 0.78. Similarly, TNF and IL6 showed moderate positive correlations with cognitive impairment scores, with correlation coefficients of r = 0.69 and r = 0.66, respectively.

In contrast, AKT1 expression showed a negative correlation with cognitive dysfunction-related measures, with r = -0.64, suggesting that reduced activation of insulin survival signaling may be associated with worsening cognitive performance. These findings support the potential role of disrupted insulin signaling and inflammatory activation in diabetes-associated Alzheimer's disease pathology.

8. Integrated Interpretation of the Shared Molecular Network

Overall, the integrated bioinformatics analysis suggests that T2DM and AD share a distinct molecular signature involving insulin signaling impairment, chronic inflammation, oxidative stress, apoptosis, and neuronal dysfunction. The identification of AKT1, GSK3B, TNF, INS, and IL6 as major hub genes highlights the importance of the PI3K/Akt/GSK3B axis and inflammatory signaling in the pathological overlap between diabetes and Alzheimer's disease.

These findings indicate that the shared molecular background of T2DM and AD extends beyond systemic hyperglycemia and may involve coordinated disruption of neuronal survival pathways, immune-inflammatory responses, and metabolic signaling networks.

Conclusion

This study provides compelling evidence that T2DM and AD share a profound genetic and regulatory overlap, centered on the dysregulation of insulin signaling and inflammatory pathways. By utilizing systems biology, we identified a robust network of 65 common genes, with AKT1, GSK3B, TNF, INS, and IL6 functioning as master regulatory hubs. These genes are not merely bystanders; they represent potential therapeutic targets for dual-action pharmacological interventions and critical candidates for future peripheral biomarkers. Ultimately, this research strengthens the concept of "Type 3 Diabetes" and provides a molecular roadmap that bridges the gap between metabolic endocrinology and neuro-geriatrics, offering new hope for integrated disease management.

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