

Association Rule Mining and Gene Expression Analysis Uncover Links between Gastroesophageal Reflux disease and Diabetes Mellitus

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ABSTRACT

Gastroesophageal reflux disease and diabetes mellitus are prevalent chronic conditions with significant global health implications. Studies suggest a strong association between the two, with DM patients exhibiting a 61% higher risk of GERD due to factors such as delayed gastric emptying, autonomic neuropathy, and poor glycaemic control. Despite clinical evidence indicating a strong association between GERD and DM, the precise molecular mechanisms and shared genetic signatures underlying this comorbidity remain poorly understood. This knowledge gap limits the development of integrated diagnostic and therapeutic strategies for patients affected by both conditions. This study aims to determine shared gene expression profiles and signalling mechanisms that regulate the relationship between GERD and DM. Using gene expression datasets from the Gene Expression Omnibus (GEO), we identified 47 DEGs in GERD (GSE9768) and 17 in DM (GSE161355) by applying a rigorous statistical threshold ($p < 0.002$). To identify gene co-expression patterns, we employed an unsupervised machine learning technique, the Apriori algorithm of association rule mining, combined with Jaccard similarity, with minimum support (0.2) and confidence (0.8). This approach identified key genes including AXL, PTGER2, LGALS3, GBP1, and CHI3L1, which appeared in multiple rules, indicating their potential involvement in both diseases. Gene ontology and pathway enrichment analysis highlighted shared biological processes, particularly related to inflammation and prostaglandin signalling. Protein-protein interaction networks and gene co-expression analysis further supported the involvement of these genes in immune regulation and tissue remodelling. Gene-disease association analysis identified strong connections between the identified genes and both GERD and DM, offering potential therapeutic targets for further investigation. These findings suggest that common molecular mechanisms, particularly inflammatory pathways, underlie the coexistence of GERD and DM, and propose these genes as biomarkers for diagnosis and treatment strategies. Future studies should focus on experimental validation to confirm these results and explore potential therapeutic interventions.

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1. Introduction

Gastroesophageal reflux disease (GERD) is a prevalent gastric condition occurs when the acidic contents of the stomach flow back into the esophagus and affects roughly 13% of the worldwide population, or up to 20% of adults in Western nations according to Richter et al [1]. GERD most commonly associated with clinical manifestations of heartburn, regurgitation, dysphagia, and chest pain with the potential for progression to complications including Barrett's esophagus and esophageal adenocarcinoma as described by Maret et al [2]. Pathogenesis of GERD involves lower esophageal sphincter dysfunction, increased gastric acid production, and esophageal acid exposure, as founded by Corley et al [3].

The American diabetes association reported that [4] diabetes mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia due to insulin resistance or impaired insulin secretion or both. This chronic condition adversely affects multiple organ systems including the kidneys, nervous system, and cardiovascular system, leading to complications such as nephropathy, neuropathy, and retinopathy. Type 1 diabetes mellitus is autoimmune mediated destruction of pancreatic β cells; type 2 diabetes mellitus involves peripheral insulin resistance and inadequate insulin secretion. Diabetes Mellitus has affected 366 million individuals worldwide in 2011, with projections indicating an increase to 552 million by 2030, as described by the International Diabetes Federation (IDF) [5].

Sun et al [6], highlighted a significant association between GERD and DM. For instance, individuals with DM have a higher prevalence of GERD symptoms and complications, with poor glycemic control and autonomic neuropathy being key contributing factors. They reported that DM patients have a 61% increased risk of GERD, with some studies suggesting delayed gastric emptying as a possible link between the two conditions. Chen J et al [7] noted the bidirectional relationship between GERD and DM, where GERD may exacerbate metabolic dysregulation. Recent advances in genomic research provide new insights into the shared molecular mechanisms of GERD and DM. Genetic studies using Mendelian randomization and genome-wide association analyses have identified overlapping pathways, including inflammation, cytokine signaling, and metabolic regulation, which may explain their co-occurrence. Functional enrichment and network analyses have revealed common genes and pathways that could serve as potential therapeutic targets.

However, despite the recent advancements, the complex gene- gene interactions and shared regulatory networks between GERD and DM remain poorly characterized. Traditional genomic analysis overlook the combinatorial nature of gene expression. There is a growing need for integrative data mining approach, such as association rule mining and multivariate covariance analysis to uncover the hidden molecular relationships and shared pathophysiological mechanism between the two diseases.

Our research article aims to investigate the genetic association between GERD and DM using multivariate covariance analysis, association rule mining (ARM), and pathway enrichment. By uncovering shared candidate genes and pathways, this study seeks to provide insights into the underlying molecular mechanisms of these diseases, offering potential targets for early diagnosis and personalized therapeutic strategies.

2. Methodology

2.1 Data Collection

Gene Expression datasets for Gastroesophageal Reflux Disease and Diabetes Mellitus were obtain from Gene Expression omnibus (GEO, <https://www.ncbi.nlm.nih.gov/geo/>) database. The dataset GSE9768 contains 11 GERD patient ad 2 healthy controls and GSE161355 dataset include 18 DM

patients and 15 non-DM patients, both generated using the GPL570 platform [HG-U133_Plus_2] Affymetrix Human Genome U133 plus 2.0 Array. Figure 1 shows the methodological approach of this study.

2.2 Identification of Differentially Expressed Genes (DEGs)

We preprocessed the raw microarray data from GERD (GSE9768) and DM (GSE161355) using the "affy" and "gcrma" package of R software (version 4.3.2). This included quantile normalization, log2 transformation, and background correction. The low expression genes was filter by using "genefilter" package, and DEGs were found by fitting linear models using Multivariate Analysis of Covariance (MANCOVA), with a tougher cutoff of $p < 0.002$ for high-confidence genes and a selection threshold of $p < 0.05$ for low-expression genes. The "hgu133plus2.db" and "pheatmap" package was used to annotate and visualize gene expression patterns, emphasizing co-expression networks and regulatory links between GERD and DM.

2.3 Association Rule Mining to Identify Common Genes between DM and GERD

Frequent gene expression patterns and correlations between DEGs in GERD and DM were found using Association Rule Mining (ARM). The "arules" package in R software (version 4.3.2) was used to implement the Apriori algorithm with a support threshold of (0.2) and confidence level (0.8), following the selection of genes with comparable expression behavior using Jaccard similarity which is set to 0.2. The CTD and DisGeNet databases served to interpret the biological significance of common genes identified in association rules. Functional enrichment and protein-protein interaction (PPI) analysis further explored their involvement in shared molecular pathways. This integrative method provided information about the genetic connections between GERD and DM.

2.4 Gene Disease Association

Gene-disease association helps in the identification of therapeutic targets and the comprehension of disease mechanisms by showing connections between particular diseases and genetic variations. We examined these relationships using PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), DisGeNet (<http://www.disgenet.org/>) and the Comparative Toxicogenomics Database (<https://ctdbase.org/>). CTD combines curated data on gene-disease and environmental interactions, while DisGeNet and PubMed provide additional biomedical literature.

2.5 Gene Ontology (GO) and Pathway Enrichment analysis

To identify the shared functions and pathways between DM and GERD, the EnrichR online tool (<https://maayanlab.cloud/Enrichr/>) was used in combination with GO (biological processes, cellular component, and molecular functions) and pathway enrichment analysis (WikiPathways, Reactome, BioCarta, and Kyoto Encyclopedia of Genes and Genomes (KEGG)).

2.6 Protein-Protein Network Analysis and Gene Co-expression

Protein-Protein Interaction of the identified common genes were studied using the STRING database (<https://string-db.org/>) with confidence scores between 4.00 to 9.00 indicating low and high levels of interaction reliability. The constructed PPI network displays proteins as nodes and their

interactions as edges with highly interconnected nodes labeled as key common genes. Additionally, GeneMANIA (<https://genemania.org>) a user-friendly platform constructs co expression network to infer gene function by integrating known and predicted relationships such as physical associations and shared pathways involvement.

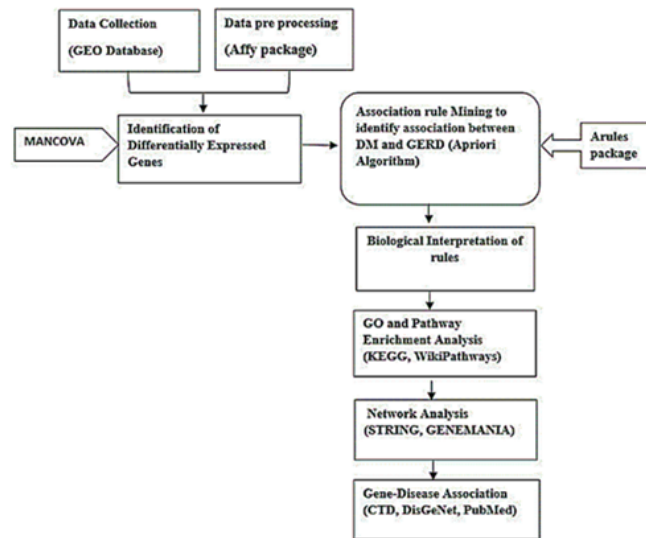


Fig. 1. The comprehensive depiction of the entire workflow

3. Results

3.1 Identification of Differentially Expressed Genes (DEGs)

The GSE9768 dataset contains 47 DEGs while the GSE161355 dataset contains 17 DEGs. Genes with p-values less than 0.05 initially qualified as significant, but a strict threshold of $p < 0.002$ guided the systematic identification of DEGs in both GERD and DM datasets. Figures 2A and 2B illustrate the heatmaps visualizations of the distribution of DEGs between patients with GERD and normal, and between DM and non-DM patients.

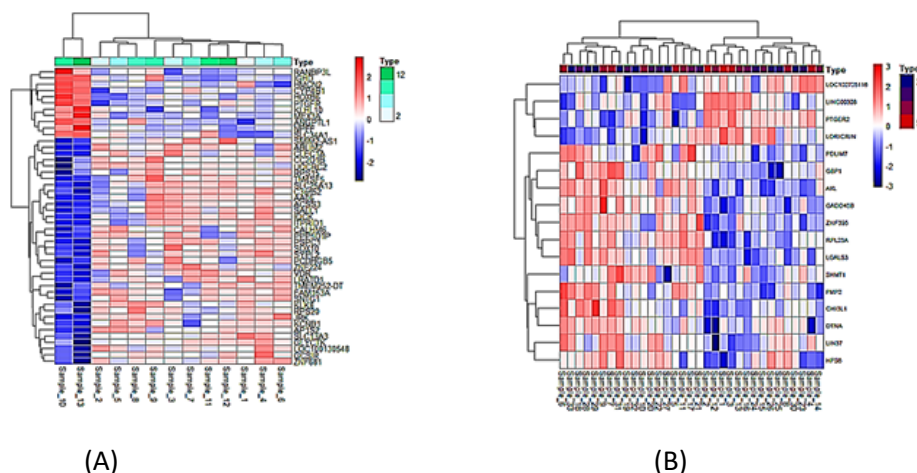


Fig. 2. Using a P-value cutoff of <0.002 , the analysis identified DEGs in (A) DM patients and (B) GERD patients. Heat map visualizations illustrate gene expression levels, with blue representing lower expression and red indicating higher expression across samples

3.2 Association Rule Mining to Identify Common Genes between DM and GERD

We selected an initial set of 1,282 rules based on Jaccard similarity, and then pruned to 88 high confidence association rules using a minimum confidence threshold of 0.8. After removing redundant rules, we obtained the final set of unique association rules, shown in Table 1. The analysis of these rules revealed robust gene co-expression patterns that may reflect potential functional relationship between implicated genes. In particular, genes as AXL, PTGER2, LGALS3, GBP1, and CHI3L1 were frequently occur in multiple rules, pointing to their important role in common immune and inflammatory pathways. Interestingly, AXL appeared in all major rules, indicating its regulatory importance, and PTGER2 and LGALS3 co-occurred in all major rules, suggesting they play roles in signaling and structural functions. Together, these data strongly support a role for CHI3L1 and GBP1 in immune regulation and tissue remodeling in both GERD and DM.

Table 1

Unique Association Rules Identified from Differentially Expressed Genes Shared between Gastroesophageal Reflux Disease and Diabetes Mellitus

Rules	Support	Confidence
1. {AXL} $\Rightarrow$ {PTGER2,UQCRC2,GBP1,ABLIM2,NPFF,MEX3A,DTNA,LGALS3,CHI3L1,ANGPTL1,RANBP3L,ITPRID1,PTGFR,ZNF224}	21%	100%
2. {CHI3L1} $\Rightarrow$ {SALL1,SLC13A3,DTNA,GCSIR,LGALS3,RPL23A,AXL}	21%	100%
3. {PTGER2} $\Rightarrow$ {AXL,UQCRC2,IGHD,NPFF,ZNF224,ITPRID1,PTGFR,MEX3A,GBP1,ANGPTL1}	21%	100%
4. {LGALS3} $\Rightarrow$ {GBP1,DTNA,AXL,GCSIR,SALL1,IQCK,SLC13A3}	21%	100%

3.3 Gene ontology (GO) and Pathway Enrichment Analysis

We used EnrichR to identify biological pathways and functional categories significantly associated with the 20 common genes between GERD and DM. Pathway enrichment using KEGG, Reactome and WikiPathways (Figure 3.) highlighted key inflammatory and metabolic signaling pathways. Notably, pathway enrichment analysis identified the COX-2/prostaglandin E2 (PGE2) inflammatory cascade. In GERD, acid –induced epithelial damage increases COX-2 expression and PGE2 production, promoting mucosal inflammation. In DM, hyperglycemia upregulates COX-2, leading to prostaglandin – mediated gastric motility issues such as gastroparesis. COX inhibitors like indomethacin have shown partial relief, supporting the role of this pathway in both conditions. These findings suggest a shared COX-2/PGE2 mechanism linking GERD and DM. The cellular response to prostaglandin stimulus (Figure 4A, GO: 0071379), cytoskeleton (Figure 4B, GO: 0005856) and prostaglandin receptor activity (Figure 4C, GO: 0004955) were the most significant GO terms in biological process, molecular function and cellular components.

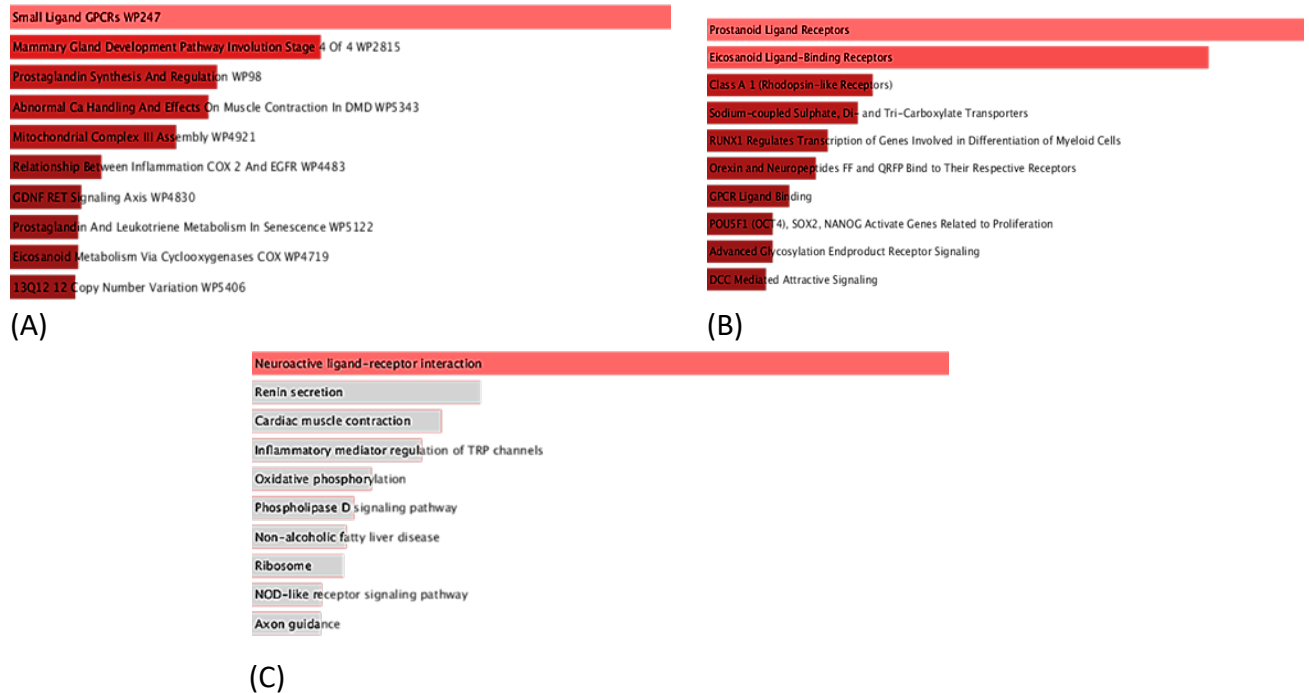


Fig. 3. Bar graphs presents the pathway analysis of genes shared between DM and GERD showing, (A) KEGG pathways, (B) Reactome and (C) WikiPathways 2024 human

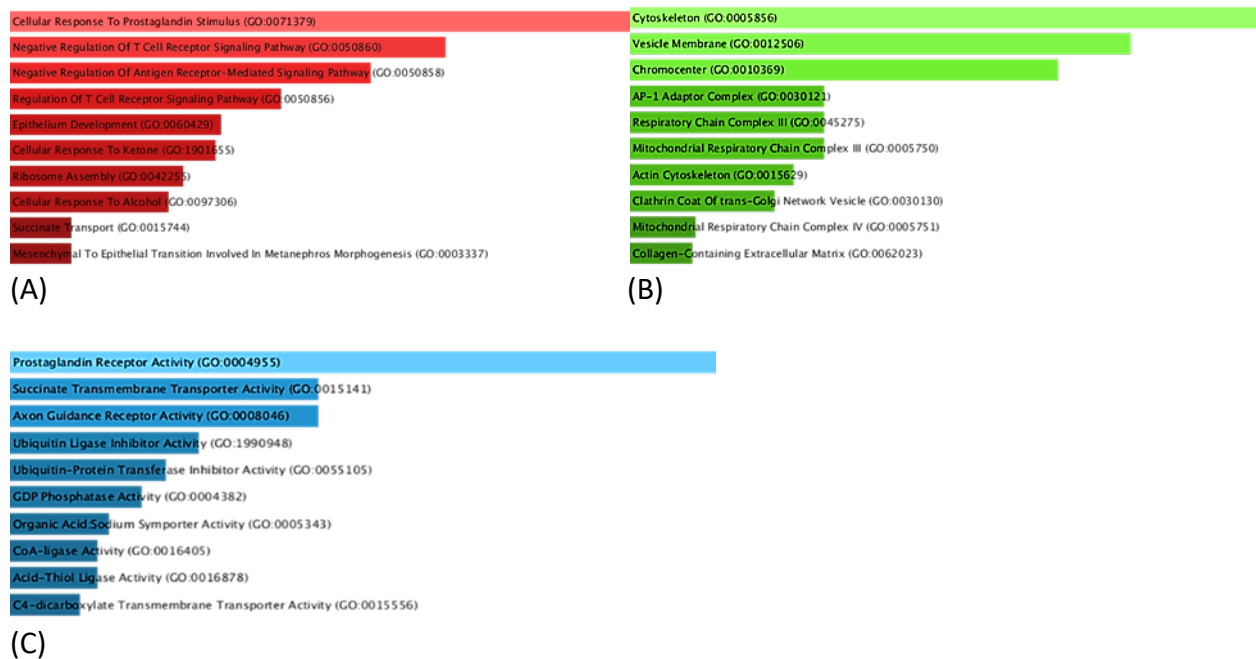


Fig. 3. Bar Graphs displays the ontological classification of shared genes between DM and GERD based on (A) biological process, (B) cellular component and (C) molecular function

3.4 PPI Network Analysis and Gene Co-expression

The shared genes in PPI network consists of 40 nodes and 95 edges, which has a PPI enrichment P value less than $1.0e-16$ (Figure 5A). We established an intricate gene interaction network using the GeneMANIA database to elucidate the biological functions of these common genes (Figure 5B), in these interactions, 28.07% are due to co-expression, 22.13% are predicted, 44% involve physical interactions, and 3.38% pertain to co-localization. The analysis also showed that these genes

primarily link to prostanoid receptor activity, the amino sugar catabolic process, cellular responses to fatty acids, and the ERK1 and ERK2 signaling cascades. These genes may act as key genes and help in the development of novel therapeutic strategies for both diseases.

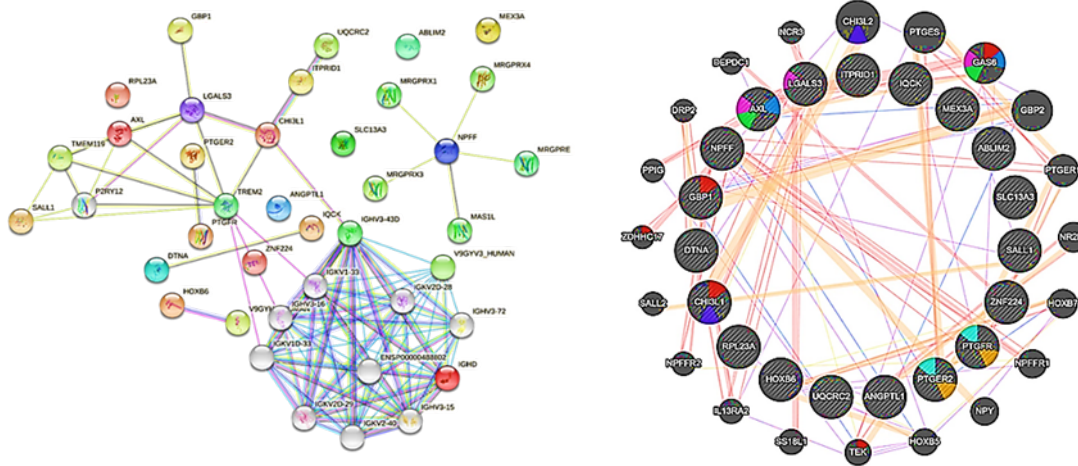


Fig. 5. (left) PPI network of associated genes between DM and GERD (right) GeneMANIA-generated gene co-expression network showing the common genes and their functionally associated co-expressed partners linked to both GERD and DM

3.5 Gene Disease Association

Genes identified through association rule mining were further evaluated for their biological relevance to DM and GERD using web-based resources, including the CTD, DisGeNet, and PubMed. We individually assessed each gene involved in the association rules by selecting “Diabetes Mellitus” and “GERD” from the disease category tab in these databases. CTD provided association data for all the identified genes (AXL, UQCRC2, GBP1, ABLIM2, NPFF, PTGER2, MEX3A, DTNA, LGALS3, CHI3L1, RANBP3L, ITPRID1, PTGFR, SALL1, SLC13A3, GCSIR, RPL23A, ZNF224, IGHD, and IQCK) based on inference and reference scores. However, DisGeNet reported associations for only six genes, while PubMed retrieved relevant literature for seven genes with both diseases. To refine the results, we selected genes commonly identified in at least two of the three databases. Notably, PubMed and DisGeNet both included most of the genes, except that NPFF and UQCRC2 appeared only in PubMed, while SALL1 appeared only in DisGeNet. Among them, NPFF showed an association with DM only, while UQCRC2 and SALL1 showed an association with GERD. The genes AXL, GBP1, PTGER2, LGALS3, and CHI3L1 emerged as common candidates, showing strong associations with both DM and GERD across all three databases. These findings highlight a set of key genes potentially involved in both diseases, providing a foundation for further functional and clinical investigation.

4. Discussion

DM and GERD are common chronic conditions that often occur together, with studies showing a strong connection between them. Complications of diabetes, such as nerve damage (autonomic neuropathy), slow stomach emptying, and issues with esophageal movement, can contribute to acid reflux and GERD symptoms. Additionally, factors like obesity and lifestyle habits may further increase the risk. Understanding the connection between these two conditions can help develop better

treatment strategies and improve patient care. This study aimed to demonstrate the association between GERD and DM through association rule mining and identify common genes that are involved in both conditions. Through critical analysis and form the best of our knowledge, this is the first study to explore the association between GERD and DM through association rule mining using R. Recent studies increasingly recognized the association between GERD and DM, showing that individuals with DM face a higher risk of GERD symptoms and complications. Poor glycemic control and autonomic neuropathy significantly contribute to these conditions. Meta-analysis studies reported by Sun *et al* [6] that DM patient's exhibit a 61% higher risk of GERD, with delayed gastric emptying proposed as a possible link. Furthermore, GERD may worsen metabolic dysregulation in DM patients, suggesting a bidirectional relationship. Recent advancements in genomic research have highlighted shared molecular mechanisms underlying GERD and DM. Mendelian randomization and genome-wide association studies (GWAS) by Chen J and Porter *et al* [7,8] have revealed overlapping genetic pathways, including those involved in inflammation, cytokine signaling, and metabolic regulation.

The analysis identified 47 DEGs from GERD dataset and 17 DEGs from DM datasets by applying p-value threshold to 0.002. We applied association rule mining to identify gene expression patterns linked to GERD and DM using the apriori algorithm and Jaccard similarity to assess the similar expression genes, with a support threshold of 0.2 and confidence of 0.8. From an initial 1282 rules, filtering based on confidence resulted in 88 unique rules after removing redundancies. The extracted rules revealed strong co-expression patterns, highlighting genes like AXL, PTGER2, LGALS3, GBP1 and CHI3L1 as key regulators in immune response, inflammation, and cellular structure regulation. Notably, these five genes frequently appeared in the highest number of rules, emphasizing their central role in the association. All 20 genes (AXL, UQCRC2, GBP1, ABLIM2, NPFF, PTGER2, MEX3A, DTNA, LGALS3, CHI3L1, RANBP3L, ITPRID1, PTGFR, SALL1, SLC13A3, GCSIR, RPL23A, ZNF224, IGHD, and IQCK) undergo further evaluation to check their role in various pathways and disease databases that linked with both conditions. Five of them (AXL, PTGER2, LGALS3, GBP1 and CHI3L1) have been involved in the pathogenic mechanism of both diseases. GERD and DM share molecular similarities, with several key genes implicated in both diseases. Through its control of metabolic and inflammatory signalling pathways, Studies by Lee CH *et al* & Hong J *et al* [9, 10] have recently stated that AXL has a critical function in the pathogenesis of both DM and GERD, hence could specify the molecular link. Endothelial dysfunction, impaired angiogenesis, and increased inflammation play a role in vascular complications in DM due to disruption of Gas6/AXL/Akt signaling pathway induced by hyperglycemia. In GERD, AXL contributes to tumor progression, chemo resistance and autophagy through the ROS-AMPK-ULK1 axis in the context of esophageal adenocarcinoma (EAC), pointing to common mechanisms inflammatory and metabolic. GBP1 contributes to disease progression in both conditions. In esophageal squamous cell carcinoma (ESCC) associated with GERD, GBP1 enhances the lymphatic metastasis and tumor invasiveness. It is involved in DM as a player in diabetic retinopathy through the processes of pyroptosis and vascular damage, tying inflammation to metabolic dysfunction stated by Li L *et al* & Wang N *et al* [11, 12]. Receptor PTGER2 for prostaglandin E2 (PGE2) has dual functions. In DM, its activation prevents β -cell loss and preserves function and insulin secretion, while its inhibition aggravates β -cell loss. In contrast, in GERD, PTGER2 enhances esophageal epithelial inflammation and remodeling by inducing cytokines (e.g., IL-6, CXCL-8) and increases mucosal barrier dysfunction describe previous studies[13, 14]. LGALS3 (Galectin-3) is elevated in both diseases. In DM, it is involved in the endothelial dysfunction, insulin resistance and atherosclerosis. Elevated serum levels correlate with mucosal inflammation in GERD and therefore have a potential use as a diagnostic test and may play a role in immune modulation demonstrated by Al-Khalidy *et al* & Milosevic J *et al* [15, 16]. Di Rosa *et al* & Huang J *et al* [17,18] reported that CHI3L1 (Chitinase-3-like protein 1) is associated with chronic inflammation and tissue remodeling in

both conditions, In DM, it promotes nephropathy and retinopathy and in GERD associated ESCC, it promotes tumor progression by recruiting macrophages and immune suppression. However, gene-disease association analysis from CTD, PubMed, and DisGeNet databases show that UQCRC2 and SALL1 are only associated with GERD, and NPFF with DM. The remaining 14 genes have no or little known association with any of the two diseases in the databases referenced.

Pathway enrichment analysis identified prostaglandin receptor signalling and COX inflammation as a shared pathogenic and inflammatory pathway between GERD and DM. In diabetes mellitus, the upregulation of COX-2 and prostaglandin receptors causes disruption of stomach motility and subsequent gastroparesis, the inhibition of COX-2 restores pacemaker activity. Several studies report that reflux exposure activates the COX-2 and PGES isoforms leading to increased PGE2 synthesis, which triggers mucosal inflammation and epithelial destruction in GERD. Additionally, PGES isoforms shows differential expression in GERD pathophysiology across normal, squamous, and adenocarcinoma cells. These findings establish Prostaglandin signalling as a shared inflammatory and functional mechanism in both disorders suggest by previous studies [19, 20].

Additionally, we explored the protein-protein interaction (PPI) network using STRING, revealing 40 nodes and 95 edges with a highly significant PPI enrichment value ($<1.0e-16$), indicating strong interactions between these genes. GeneMANIA analysis further confirmed functional connections among these genes through co-expression (28.07%), predicted interactions (22.13%), physical interactions (44%), and co-localization (3.38%). These findings suggest that shared molecular mechanisms, including prostanoid receptor activity, amino sugar catabolic processes, and the ERK1/ERK2 cascade, may contribute to both GERD and DM pathogenesis. The identification of these common genetic markers not only strengthens the evidence of a molecular link between GERD and DM but also suggests that these genes could serve as diagnostic candidate for targeted therapy. Future studies should focus on validating these findings through experimental approaches such as gene knockdown studies, functional assays, and animal models to further investigate the precise molecular mechanisms underlying the GERD-DM association and explore potential therapeutic strategies for managing these interconnected conditions.

5. Conclusions

This study demonstrate the strong molecular association between GERD and DM through shared genes and enriched inflammatory pathways particularly prostaglandin signaling. Genes such as AXL, PTGER2, LGALS3, GBP1, and CHI3L1, appear to mediate common biological processes like inflammation, immunological control, and tissue remodeling, which supports their potential as biomarkers and therapeutic targets. Additional verification through experiments utilizing cell cultures and in vivo models is necessary to confirm these findings and investigate novel therapies for patients diagnosed with both conditions.

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