Original Article

Identifying Key Biomarkers in Celiac Disease through Analysis of Microarray Data

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Abstract

Background: Celiac disease (CeD) is a chronic autoimmune condition induced by the consumption of gluten, affecting about 1.4% of the global population. The current diagnostic methods largely rely on serological testing, which may disregard certain biomarkers that are essential for an accurate diagnosis. The objective of the present investigation is to identify significant candidate biomarkers in CeD through using a bioinformatics analysis of microarray data. **Methods:** We analyzed three datasets of the Gene Expression Omnibus database (GSE112102, GSE113469, and GSE164883) to conduct a comprehensive bioinformatics approach. We performed a meta-analysis of differentially expressed genes (DEGs), constructed gene ontology and pathway analyses, and developed protein–protein interaction networks to identify and analyze hub genes and their associated miRNAs. **Results:** We detected 165 DEGs (79 upregulated and 86 downregulated). Five key hub genes – STAT1, CDC20, perforin-1, CCL2, and MYC were identified as critical regulators involved in controlling both immune system activity and cell cycle progression. Significantly, important miRNAs, including hsa-miR-155-5p, hsa-miR-145-5p, hsa-miR-18a-5p, hsa-miR-34a-5p, hsa-miR-24-3p, and hsa-miR-146a-5p, were seen to have significant interactions with these hub genes. This emphasizes their potential involvement in the pathogenesis of CeD. **Conclusion:** The genes identified offer potential as key biomarkers for diagnosing CeD and understanding its molecular mechanisms, creating the path for improved diagnostic and therapeutic strategies.

Keywords: *Bioinformatics, biomarker, celiac disease, gene expression profiling, microarray analysis, systems biology*

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Introduction

Celiac disease (CeD) is a chronic autoimmune condition initiated by the ingestion of gluten, primarily found in wheat, barley, and rye.[1] Gluten ingestion in susceptible individuals causes intestinal mucosal damage, resulting in gastrointestinal symptoms such as diarrhea, nausea, anorexia, abdominal pain, and vomiting, as well as extraintestinal symptoms including fatigue and weight loss.[2] Recent studies estimate that CeD affects about 1.4% of the global population (95% confidence interval 1.1–1.6) as of 2024.[3] Individuals with genetic or autoimmune disorders, such as type 1 diabetes, autoimmune thyroid disease, dermatitis herpetiformis, and selective immunoglobulin (Ig) A deficiency, have an increased susceptibility to CeD. Moreover, first-degree relatives of CeD patients exhibit higher risk compared to the general population.[4]

Patients with CeD commonly carry human leukocyte antigen (HLA)-DQ2 or HLA-DQ8, essential receptors on antigen-presenting cells (APCs), predisposing them to the disease.[5] Immunological reactions to gluten in CeD patients trigger the production of highly specific autoantibodies, notably antitissue transglutaminase IgA (tTG-IgA), antiendomysial IgA, and antideamidated gliadin peptide IgG, which mediate small intestinal injury.[6] Currently, the primary and effective treatment for CeD is strict lifelong adherence to a gluten-free diet. Delayed diagnosis or noncompliance with dietary restrictions can lead to severe complications, including intestinal malignancy, infertility, and osteoporosis.[7,8]

Diagnosis typically relies on serological tests combined with invasive duodenal biopsy. Although biopsy remains the gold standard,

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its invasive nature has encouraged the development of less invasive serological alternatives such as tTG-IgA testing, recommended by current guidelines for both adults and children.[9,10] Taken together, these diagnostic limitations underscore the need for a genome-wide search for novel, minimally invasive biomarkers that can complement current serology and reduce reliance on biopsy.

Recent genetic studies on CeD employed methods such as exome sequencing, SNP genotyping, and epigenetic analyses, elucidating various genetic factors involved.[11] However, research exploring gene expression patterns as potential diagnostic biomarkers remains limited. This study aims to identify critical genes and miRNAs associated with CeD by meta-analyzing gene expression microarray datasets using bioinformatics, exploring their roles in CeD pathogenesis and their potential as diagnostic biomarkers.

Materials and Methods

Data acquisition and eligibility criteria for selecting gene expression datasets in meta-analysis

This study aimed to identify differentially expressed genes (DEGs) in CeD using a meta-analysis approach. Microarray datasets were obtained from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/gds/) using the keywords "Celiac disease," "Homo sapiens," and "Expression profiling by array." The search was conducted on December 17, 2023, and was restricted to studies published in the last 10 years (January 2014–December 2023). Inclusion criteria consisted of human case–control studies involving untreated patients, employing gene expression profiling methods, and providing complete raw and processed microarray data. Exclusion criteria were review articles, meta-analyses, letters, abstracts, case reports, studies using cell lines or reverse transcription–polymerase chain reaction alone, absence of a clear case–control design, or studies assessing treatment effects. All retrieved datasets were manually screened based on these criteria. Datasets were retained only if they provided complete processed probe-level data (i.e., series matrix files). Since all included datasets were generated using the Illumina HumanHT-12 platform, series matrix files were sufficient for normalization and analysis.

The overall selection workflow is detailed that 26 datasets were retrieved, 6 met the inclusion criteria, and 3 passed quality control for meta-analysis [Figure 1]. The transcriptomic profiles identified through meta-analysis were compared between CeD patients and healthy controls and subsequently analyzed for enriched pathways and regulatory networks.

Data extraction and processing

Relevant information, including GEO accession numbers, number of patients and controls, specimen sources, and platforms, was extracted from the selected studies. GSM accession numbers were compared across datasets and found to be unique; no duplicate samples were detected. Series matrix files were obtained from GEO, and probes were standardized using common Entrez IDs. All three studies used the Illumina HumanHT-12 v4 bead-chip (GPL10558); probes were therefore collapsed 1:1 to Entrez IDs with no cross-platform remapping. Because all three included datasets were generated on the same single-channel platform – Illumina HumanHT-12 v4 bead-chip (GPL10558), each probe set maps one-to-one to an Entrez Gene ID; therefore, no additional cross-platform remapping or probe-matching steps were required.

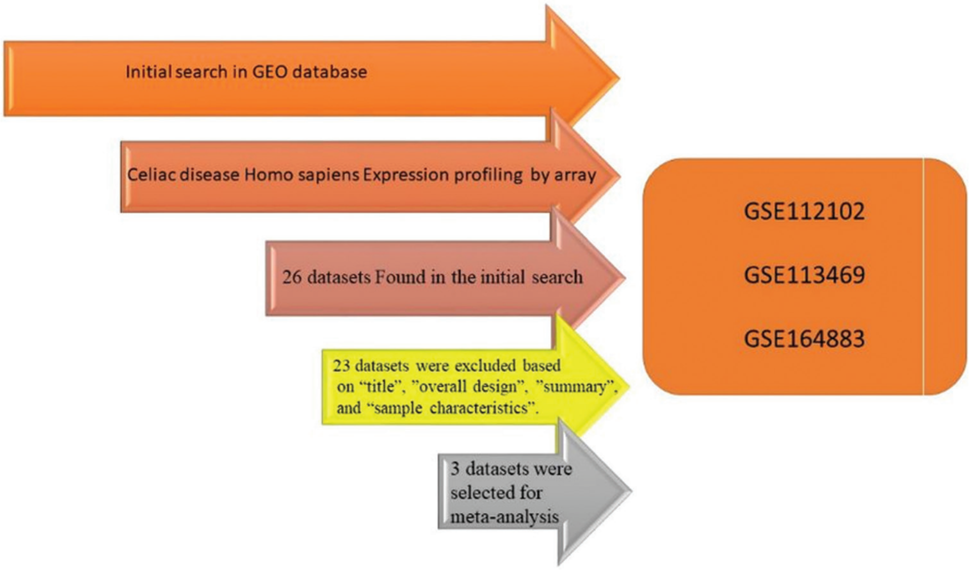

Figure 1: Dataset selection flow chart showing that a total of 26 data sets from Gene Expression Omnibus were evaluated. Finally, 3 datasets for mRNA were selected to be included in this meta-analysis. GEO – Gene Expression Omnibus

Before meta-analysis, datasets underwent normalization using log2 transformation and quantile normalization to ensure data consistency. Normalized datasets were merged using the Hughey and Butte pipeline.[12] This elastic-net meta-analysis pipeline applies empirical Bayes batch correction, probe-level scaling, and regularized regression to derive consensus expression estimates across studies,[12] followed by correction of batch effects with the ComBat method (sva package v3, Bioconductor). Batch-correction quality was verified by visual inspection of boxplots, comparing expression value distributions before and after correction. Finally, integrated datasets were reduced to a common set of probes across all platforms, ensuring uniformity and comparability of data for meta-analysis.

Meta-analysis of datasets

To accurately identify DEGs, a meta-analysis was conducted using R statistical software. Differential expression analysis was performed by applying linear modeling methods in the limma package, comparing samples categorized as "celiac" or "normal."[13] Benjamini and Hochberg's false discovery rate adjustment method was employed to control multiple testing.[14] Genes with an adjusted $P < 0.05$ and fold change (FC) >1.3 (upregulated) or <1/1.3 (downregulated) were considered significant DEGs. In addition, significant DEGs were visualized using enhanced volcano plots and heatmaps generated by Heatmapper software (https://www.heatmapper.ca), providing clear graphical representation of gene expression patterns across analyzed datasets. Because all three datasets were produced on the same Illumina HumanHT-12 v4 platform and were batch-corrected with ComBat, visual inspection of per-study effect sizes showed concordant directionality for >95% of DEGs; formal heterogeneity statistics (Q, I^2) were therefore deemed unnecessary, and a fixed-effect model was applied.

Gene ontology

Gene ontology (GO) enrichment analysis categorizes genes into biological processes (BP), molecular functions (MF), and cellular components (CCs). We conducted GO enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses of identified DEGs using the Enrichr database (https://maayanlab.cloud/Enrichr/). Clusters containing at least three genes with a GO tree interval range of 3–8 and kappa score ≥0.4 were analyzed. Pathways with $P < 0.05$ were considered statistically significant and subsequently analyzed in detail.

Construction of protein–protein interaction networks, clustering of network modules, and detection of central hub genes

A protein–protein interaction (PPI) network was constructed using the STRING database (http://string-db.org) with a confidence score >0.4. Visualization and analysis were performed using Cytoscape 3.7.1 (http://www.cytoscape.org). Hub genes were identified using cytoHubba based on three centrality measures: closeness, betweenness, and degree. Genes with a degree >10, K-core >2, and max depth >100 were considered hub genes. Cluster identification within the PPI network was performed using the Molecular COmplex DEtection (MCODE) tool with predefined parameters (degree cutoff = 2, node score cutoff = 0.2, k-core = 2, and max depth = 100). A Venn diagram (http://bioinformatics.psb.ugent.be/webtools/Venn/) was used to identify shared hub genes across different methods.

Hub gene validation

The diagnostic potential of hub genes in CeD was assessed using receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) was calculated to compare their predictive value. This analysis was conducted using GraphPad Prism v9.1.0 (GraphPad Software, Siemens Company), providing statistical assessment and visualization of hub gene performance in distinguishing CeD from healthy controls.

Evaluation of the miRNA–hub gene interaction network

Targeted miRNAs associated with hub genes were identified using miRTarBase (https://www.mirtarbase.cuhk.edu.cn/), TargetScan (http://www.targetscan.org/), and miRWalk (http://mirwalk.umm.uni-heidelberg.de/). The miRNA–hub gene interaction network was visualized using the miRNet database (https://www.mirnet.ca/) to explore regulatory relationships.

Results

Characteristics of datasets included in the analysis

Following rigorous screening, three GEO datasets (GSE112102, GSE113469, and GSE164883) met the inclusion criteria. All datasets were generated using the GPL10558 platform (Illumina HumanHT-12 V4.0 expression bead chip). A total of 121 samples (66 normal and 55 celiac) were analyzed, derived from peripheral blood mononuclear cells and mucosal biopsies. The dataset characteristics are summarized in Table 1.

Table 1: Characteristics of each selected microarray dataset for the meta-analysis

GEO accession number	Sample (normal/celiac)	Sample source	Platform	Reference
GSE113469	37 (20/17)	PBMCs	GPL10558	[15]
GSE112102	36 (24/12)	Mucosal biopsies	GPL10558	[16]
GSE164883	48 (22/26)	Mucosal biopsies	GPL10558	[17]

GEO – Gene Expression Omnibus; PBMCs – Peripheral blood mononuclear cells

Identification of common differentially expressed genes in celiac disease

Three microarray datasets were meta-analyzed using R software, identifying 165 DEGs, including 79 upregulated and 86 downregulated genes. DEGs were visualized with an enhanced volcano plot and a heatmap [Figure 2]. Among the upregulated genes, LAX1 showed the highest FC = 1.94, whereas TDRD1 had the lowest FC (0.58) among the downregulated genes. A detailed list of significant DEGs is presented in Table 2.

Gene ontology enrichment and pathway analysis

GO analysis revealed that DEGs were significantly enriched in BP, including the cellular response to interferon-gamma (IFN-γ), defense response to the virus, and JAK-STAT receptor signaling [Figure 3a]. Enriched MF involved MHC Class Ib protein binding and double-stranded RNA binding [Figure 3b]. CC analysis highlighted the spindle and nuclear lumen [Figure 3c].

Table 2: Expressional profiles for top up- and downregulated differentially expressed genes identified by meta-analysis

Upregulated			Downregulated		
Genes	FC	Adjusted (*P*)	Genes	FC	Adjusted (*P*)
LAX1	1.94	1.09×10^{-6}	TDRD1	0.58	4.68×10^{-5}
CCR2	1.90	7.01×10^{-9}	HIF1A	0.59	1.08×10^{-12}
CDC20	1.85	8.59×10^{-6}	TSC22D2	0.59	1.63×10^{-14}
PRF1	1.80	7.23×10^{-5}	GABARAPL1	0.60	1.21×10^{-7}
HCP5	1.63	2.57×10^{-8}	CYP3A4	0.61	0.000825
GBP1	1.54	0.00016	LYPLA1	0.62	9.52×10^{-8}
STAT1	1.51	0.00076	FCAR	0.62	8.41×10^{-8}
OAS2	1.48	5.44×10^{-5}	CCL2	0.63	0.016685
MYC	1.43	8.81×10^{-7}	FUT6	0.64	0.00013
IFI44L	1.42	7.51×10^{-7}	PNPLA4	0.65	0.00010

Genes were ranked by combined FC and Adjusted *P* value.
FC – Fold change

KEGG analysis indicated enrichment in NOD-like receptor (NLR) signaling, Epstein–Barr virus infection, and influenza A pathways [Figure 3d]. Reactome analysis showed involvement in interleukin (IL)-4 and IL-13 signaling and developmental biology [Figure 4].

Protein–protein interaction network construction and hub gene extraction

The PPI network of DEGs consisted of 119 nodes and 442 edges, with an average clustering coefficient of 0.450 [Figure 5]. The top 10 hub genes are summarized in Table 2. Among them, STAT1, CDC20, perforin-1 (PRF1), CCL2, and MYC were consistently identified across degree, closeness, and betweenness centrality methods, indicating their potential significance in CeD pathogenesis [Figure 6].

Identification of hub genes using molecular complex detection clustering analysis

Significant modules in the PPI network were identified using MCODE, with a threshold score >5. The primary hub cluster consisted of 34 nodes and 117 edges, with an MCODE score of 21.015. The top hub genes, STAT1, CDC20, CCL2, PRF1, and MYC, were consistently identified across MCODE and centrality-based analyses [Figure 7].

Validation of hub genes

The prognostic value of shared hub genes was assessed using ROC curve analysis. All five hub genes demonstrated significant potential for CeD prediction, with AUC values ranging from 0.7 to 0.9, indicating strong discriminative power [Figure 8].

Identification of miRNA–hub gene interactions

Interactions between shared hub genes and miRNAs were identified using TargetScan, miRTarBase, and miRWalk. The analysis revealed significant interactions with miR-155-5p, miR-145-5p, miR-18a-5p, miR-34a-5p,

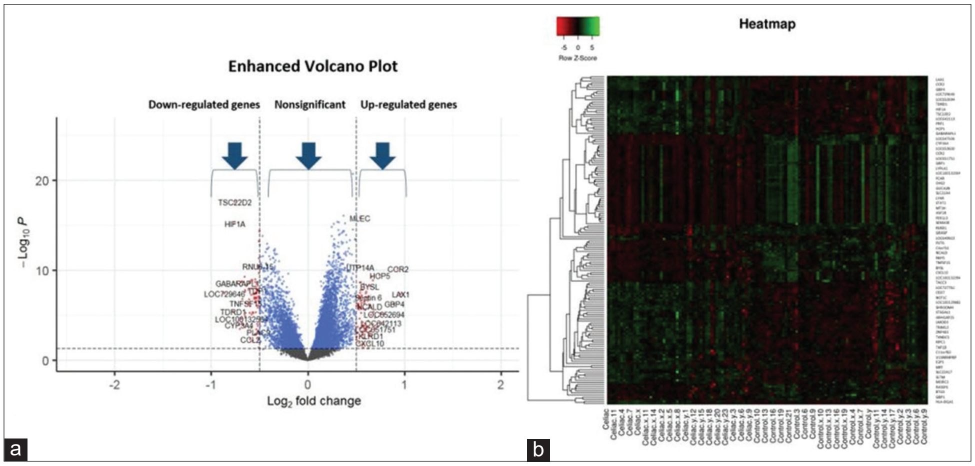

Figure 2: (a) The volcano plot showing the upregulated and downregulated differentially expressed genes (DEGs) of the celiac and normal groups. The X-axis represents the log2-fold change (FC), and the Y-axis represents log10 (P values). (b) Heatmap of the DEGs with a significant FC. Red: Upregulation; Green: Downregulation

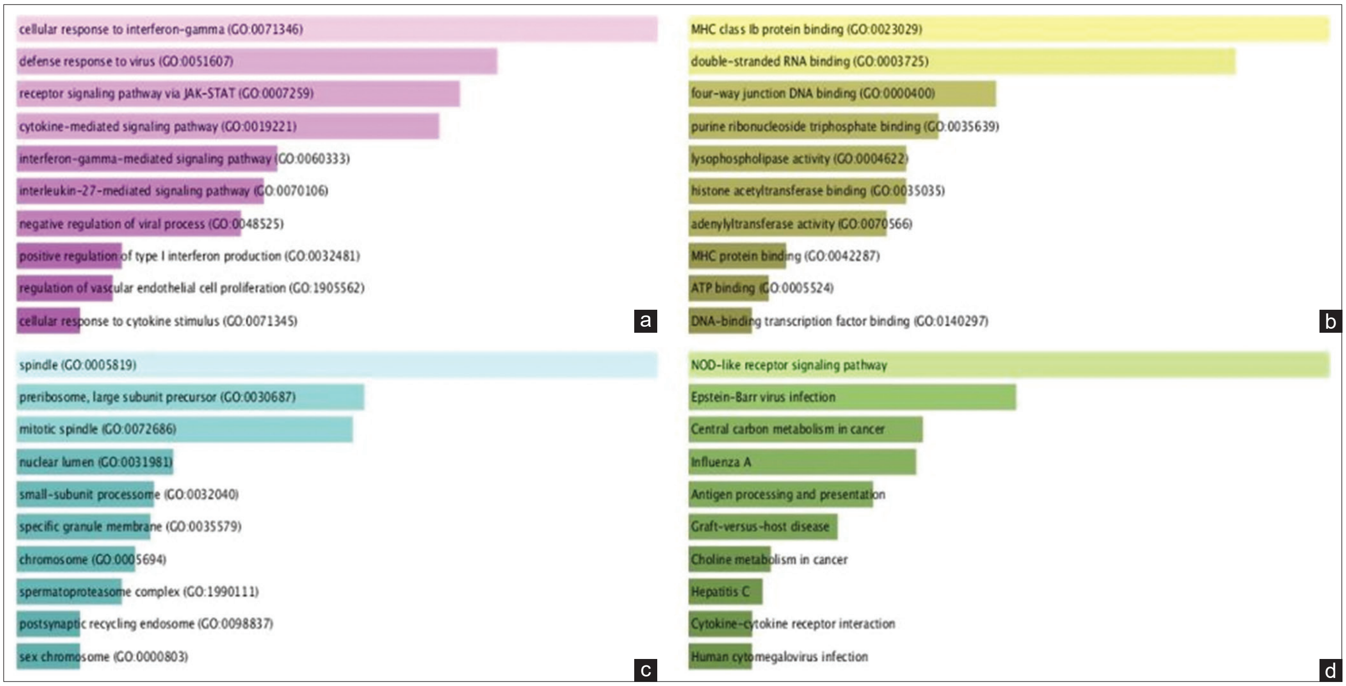

Figure 3: (a) Top 10 of biological process. (b) Top 10 of molecular function. (c) Top 10 of a cellular component. (d) Top 10 of Kyoto Encyclopedia of genes and genomes pathway enrichment

Figure 4: Top 10 integrated pathways relied on Reactome analysis

miR-24-3p, and miR-146a-5p, suggesting their regulatory role in CeD pathogenesis [Figure 9].

Discussion

CeD is a complex, multifactorial autoimmune disorder triggered by gluten ingestion. While serological markers and genetic predisposition are established diagnostic criteria, identifying novel biomarkers remains crucial for early detection and personalized treatment. This study employed a meta-analysis of microarray datasets to identify DEGs and miRNAs implicated in CeD pathogenesis.[18,19]

Pathway enrichment converged on three immune axes that together explain much of CeD pathology: (i) activation of NLR signaling, (ii) a robust IFN-γ response, and (iii) modulation by the IL-4/IL-13 cytokine axis. NLR engagement can initiate innate defenses and promote IFN-γ production, while IL-4/IL-13 reshape epithelial immunity by enhancing antigen presentation. Focusing on these interconnected pathways provides a mechanistic narrative for the transcriptomic changes, rather than a catalogue of individual GO or KEGG terms.[14,20-22]

Our analysis identified five hub genes, STAT1, CCL2, PRF1, CDC20, and MYC, consistently associated with CeD. STAT1 plays a pivotal role in JAK-STAT signaling, regulating immune responses, apoptosis, and cytokine signaling. Dysregulation of STAT1 expression may contribute to aberrant immune activation in CeD. Elevated STAT1 phosphorylation in THP-1 macrophages suggests its role

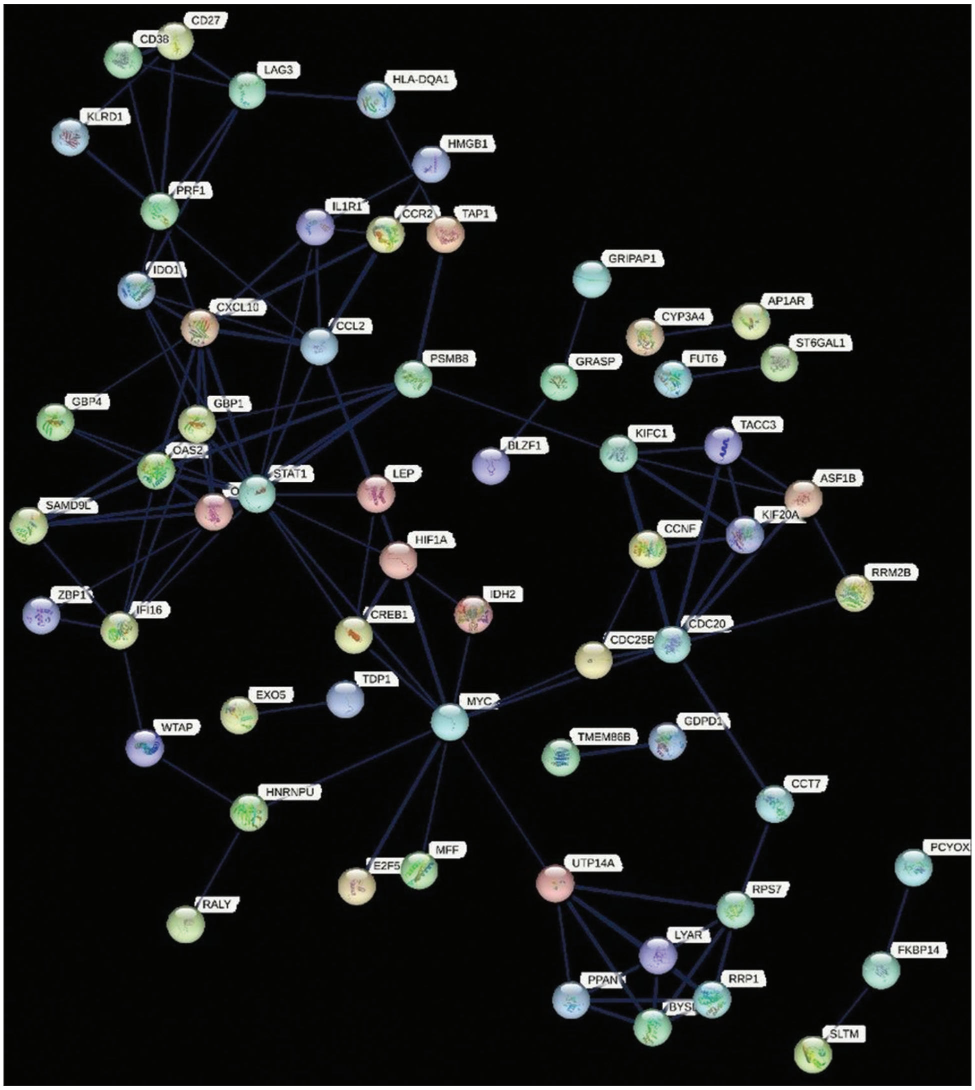

Figure 5: Protein–protein interaction (PPI) network in which nodes represent proteins, and edges represent interactions. According to this network, 10 Hub-genes (degree >10) were extracted in Cytoscape. Differentially expressed genes PPI network, the density of the network nodes is based on string confidence score >0.4

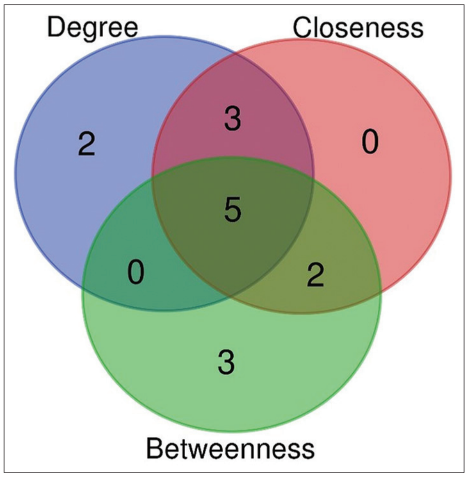

Figure 6: This Venn panel showing the overlap hub genes between the three methods (degree, closeness, and betweenness); 5 genes are common between these methods

in modulating IFN-γ signaling. Moreover, STAT1-deficient models highlight its influence on chemokine regulation, particularly CCL2, further supporting its role in disease pathogenesis.[23,24]

CCL2 (MCP-1) encodes a chemokine involved in monocyte recruitment and inflammatory response. While some studies reported reduced CCL2 expression in CeD patients adhering to a gluten-free diet, others observed increased levels in active disease. These discrepancies could result from variations in disease stage, population characteristics, or methodological differences.[25]

PRF1 is crucial for cytotoxic T-cell and NK-cell activity, mediating the destruction of infected or malignant cells. PRF1 dysregulation has been implicated in autoimmune disorders and cancer, with increased expression in CeD suggesting enhanced cytotoxic activity. Notably, elevated

PRF1 expression in cytotoxic lymphocytes upon tumor exposure reinforces its immunoregulatory role.[26]

CDC20 may act as an important regulator of the cell cycle, interacting with the anaphase-promoting complex (APC/C) to control mitotic progression. Its upregulation has been linked to multiple cancers, and recent findings suggest a role in CeD through inflammatory pathways, particularly NF-κB activation. CDC20's involvement in both CeD and familial adenomatous polyposis networks suggests overlapping mechanisms of dysregulated cell proliferation.[27]

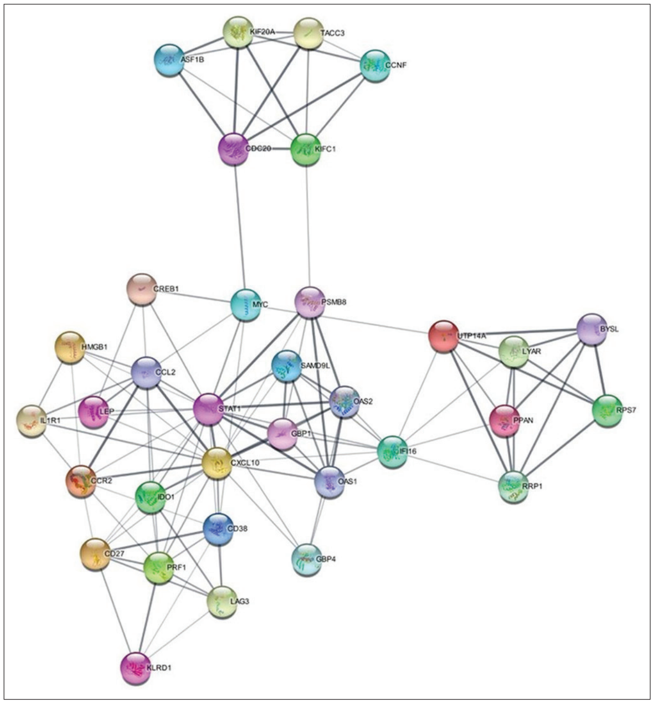

Figure 7: Cluster modules extracted by molecular complex detection demonstrated the significant hub genes

MYC functions as a transcription factor regulating metabolism, cell growth, and ribosome biogenesis. Dysregulated MYC expression is a hallmark of cancer, and recent studies suggest its involvement in autoimmune diseases such as psoriasis and myasthenia gravis. Elevated MYC expression in CeD biopsies highlights its potential role in aberrant mucosal proliferation and disease progression.[11]

miRNA analysis identified miR-155-5p, miR-145-5p, miR-18a-5p, miR-34a-5p, miR-24-3p, and miR-146a-5p as key regulators of CeD-associated genes. Notably, miR-155-5p exhibited strong interactions with four hub genes (CCL2, MYC, PRF1, and CDC20). This miRNA is known to modulate interferon responses and immune regulation. Upregulated miR-155-5p expression in CeD may contribute to immune dysregulation by altering intestinal permeability and inflammatory responses.[28]

Loss of miR-155 has been linked to reduced CCL2 expression and impaired microglial activation, further supporting its role in CeD pathology. In addition, STAT1 and miR-155-5p were identified in regulatory feedback loops across multiple cancers, reinforcing their interplay in inflammatory pathways. Overexpression of miR-155 has also been associated with reduced PRF1/NKG2D expression in NK cells, highlighting its impact on cytotoxic function.[29]

Other miRNAs, including miR-145-5p, miR-18a-5p, and miR-34a-5p, exhibited interactions with multiple hub

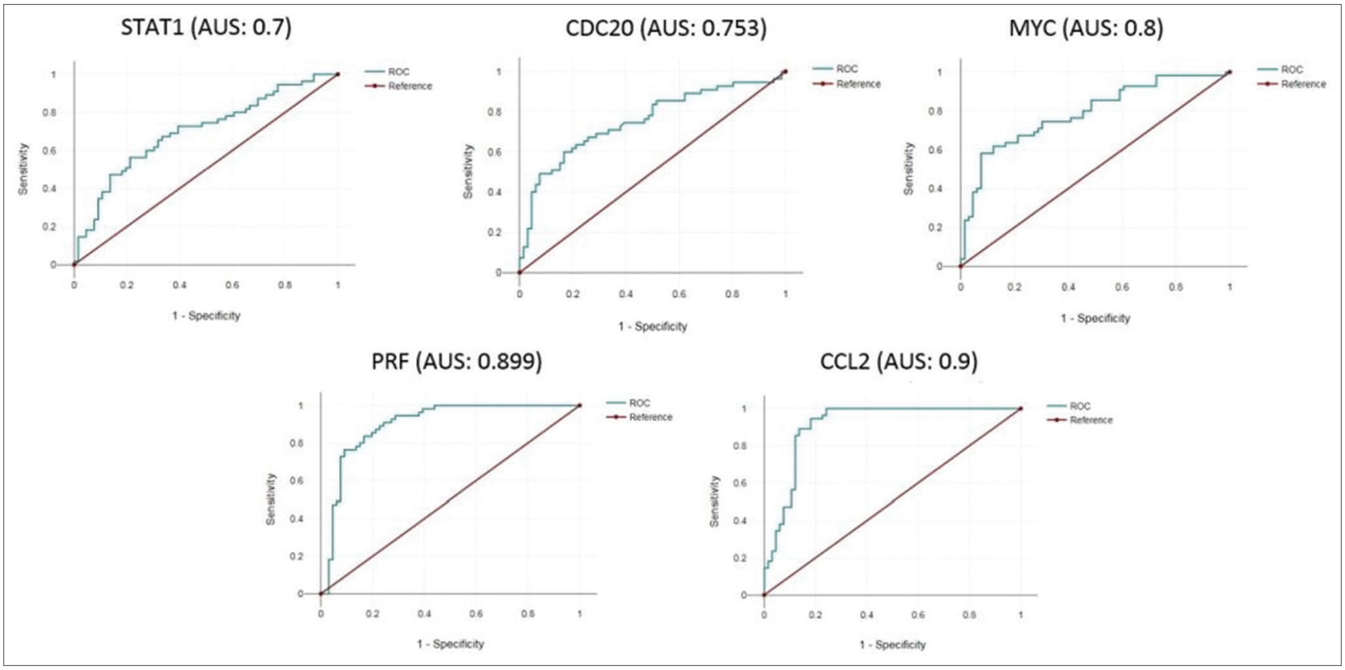

Figure 8: Evaluation of sensitivity and specificity of hub genes in the diagnosis of celiac disease. Based on the receiver operating characteristic curves, all 5 hub genes have the proper sensitivity and specificity to diagnose celiac disease

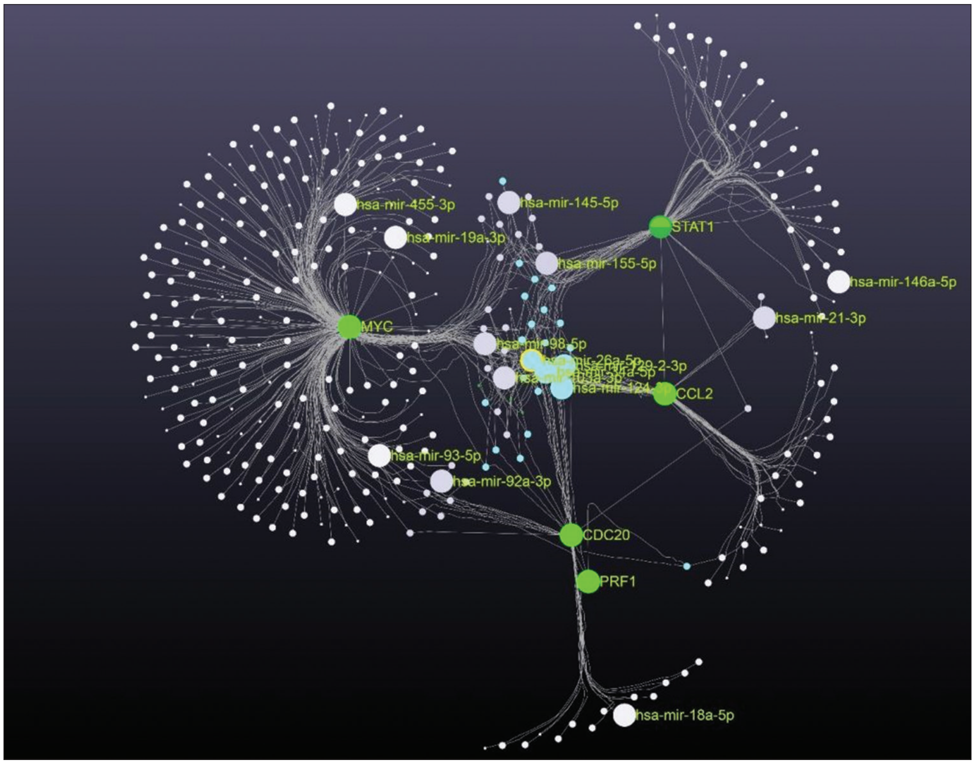

Figure 9: miRNA–hub gene interactions

genes, suggesting their involvement in CeD pathogenesis. Notably, miR-34a-5p regulates apoptosis and immune signaling, while miR-146a-5p modulates inflammatory pathways through STAT1 interactions. These findings suggest that CeD development is influenced by a complex interplay of genetic and epigenetic factors.[30]

Conclusion

Our study highlights potential diagnostic biomarkers and therapeutic targets for CeD. The identification of STAT1, CCL2, PRF1, CDC20, and MYC, along with their associated miRNAs, provides a foundation for future research. While the current CeD diagnosis relies on serological markers and biopsy, incorporating transcriptomic and miRNA-based biomarkers could enhance diagnostic precision.

Future studies should focus on functional validation of identified biomarkers through experimental models, clinical cohort studies to assess their diagnostic performance, and investigations into their therapeutic potential. These findings provide a basis for future functional studies and may ultimately inform improved diagnostic and therapeutic approaches.

Ethical approval

This study did not involve human participants, animal subjects, or identifiable personal data. Therefore, ethical approval was not required.

Funding

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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