Journal of Environmental Biology
p-ISSN: 0254-8704 • e-ISSN: 2394-0379 • CODEN: JEBIDP

JEB®

Original Research Paper
Volume 47 Issue 4 July 2026 pp. 998-1006
DOI: http://doi.org/10.22438/jeb/47/4(SI)/SPL-20

J. Environ. Biol., 2026

Journal website : www.jeb.co.in ★ E-mail : editor@jeb.co.in

Genetic and pathway analysis of Sjögren's Syndrome: Insights from top 30 associated genes

A. Dharaneedhar[1]*, K.M. Jyothi[1], E.V. Ravikanth[2], G.M. Chowdary[1] and U. Adiga[3]

[1]*Department of General Medicine, Apollo Institute of Medical Sciences and Research Chittoor, Murukambattu - 517 127, India*
[2]*Department of Dermatology, Apollo Institute of Medical Sciences and Research Chittoor, Murukambattu - 517 127, India*
[3]*Department of Biochemistry, Apollo Institute of Medical Sciences and Research Chittoor, Murukambattu - 517 127, India*

Received: 29 November 2025 **Revised:** 04 May 2026 **Accepted:** 04 June 2026

***Corresponding Author Email:** dharaneedhar_a@aimsrchittoor.edu.in ***ORCiD:** https://orcid.org/0009-0005-8310-3850

Abstract

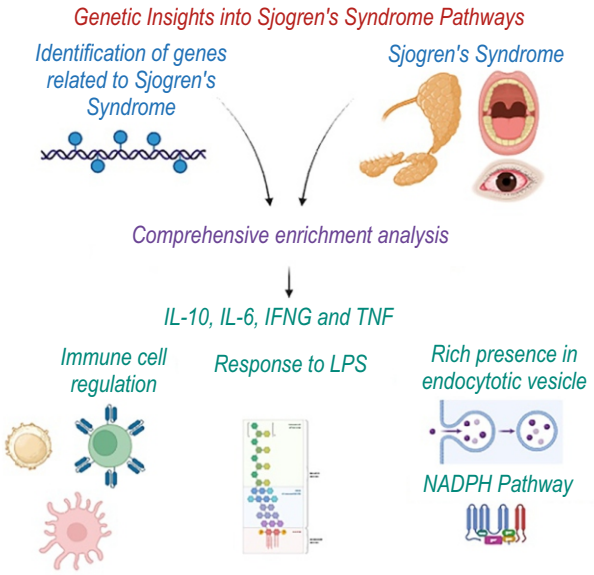
Aim: Sjögren's syndrome (SS) is an autoimmune disorder where immune cells infiltrate the body's moisture-producing glands. The top 30 genes associated with the development of Sjögren's syndrome were retrieved from the DisGeNET database to characterize the biological processes, cellular components and molecular functions implicated in disease pathogenesis.

Methodology: The top 30 VSD-associated genes from DisGeNET were subjected to comprehensive GO, pathway, transcription factor, and metabolite enrichment analyses, with visualizations generated using R (v4.4.2).

Results: The biological processes that came up most often involved immune regulation, inflammatory responses, and cytokine signaling. These genes were mostly located in extracellular regions and at immunological synapses. The most significant molecular functions were cytokine activity and receptor binding. When we looked at pathways, immune infiltration and allograft rejection really stood out. Metabolite analysis connected Sjögren's syndrome genes with simvastatin and inflammatory markers, while drug effects were linked to bone marrow.

Interpretation: This study points to a strong immune component in SS and highlights IL-10, IL-6, IFNG, and TNF as genes worth investigating further. Modulation of these cytokines may facilitate precision medicine approaches and more targeted therapeutic strategies for Sjögren's syndrome.

Key words: Autoimmunity, Cytokine signaling, Gene enrichment, Inflammation, Sjögren's syndrome



How to cite: Dharaneedhar, A., K.M. Jyothi, E.V. Ravikanth, G.M. Chowdary and U. Adiga: Genetic and pathway analysis of Sjögren's Syndrome: Insights from top 30 associated genes. *J. Environ. Biol.*, **47,** 998-1006 (2026).

Introduction

Sjögren's syndrome is a chronic autoimmune disease that mainly attacks the body's moisture-producing glands. It has a complex immune basis involving problems with both T-cells and B-cells. Changes in T-cell populations—particularly too many T helper (Th)17 cells and regulatory T-cells (Tregs) that don't work properly—lead to ongoing inflammation, tissue damage and production of autoantibodies (Hu *et al.,* 2025). At the same time, B-cells become overactive, which shows up as high antibody levels in the blood, the creation of autoantibodies like anti-SSA/Ro and anti-SSB/La, and an increased risk of B-cell lymphomas, including mucosa-associated lymphoid tissue (MALT) lymphoma (Tian *et al.,* 2021).

The epidemiology of Sjögren's syndrome reveals a striking female predominance, with women accounting for approximately 90% of affected individuals, and peak incidence occurring in the fourth and fifth decades of life (Diggins and Weller, 2026). The global prevalence is estimated between 0.01% and 0.72%, though underdiagnosis is common due to the insidious onset and overlap with other autoimmune conditions (Jin *et al.,* 2023). Primary Sjögren's syndrome arises independently, while secondary Sjögren's syndrome develops in the context of pre-existing autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus (Negrini *et al.,* 2022). The diagnosis is typically established through a combination of clinical criteria, serological markers including anti-SSA/Ro and anti-SSB/La antibodies, and histopathological evaluation of minor salivary gland biopsies demonstrating focal lymphocytic sialadenitis (Zhao *et al.,* 2024). The considerable delay between symptom onset and diagnosis, often exceeding five years, underscores the clinical complexity of the condition and the urgent need for reliable molecular biomarkers.

Cytokines play a central part in the development of Sjögren's syndrome. Pro-inflammatory molecules like tumour necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-6, and IL-17 amplify tissue inflammation and damage, while regulatory cytokines like IL-10 try to calm things down (Soyfoo and Nicaise, 2021). When there's an imbalance between these pro-inflammatory and regulatory cytokines, it leads to chronic inflammation and progressive destruction of the moisture-producing glands (Mihaescu *et al.,* 2025). Clinically, Sjögren's syndrome can range from mild dryness symptoms to severe problems affecting the whole body, including blood vessel inflammation, nerve damage and lung issues (Bowman, 2026). Furthermore, patients face an ongoing risk of developing non-Hodgkin lymphoma, particularly mucosa-associated lymphoid tissue (MALT) lymphoma, which significantly affects their health and survival (Mallick *et al.,* 2025).

The genetic architecture of Sjögren's syndrome involves both major histocompatibility complex (MHC) and non-MHC loci. Genome-wide association studies have identified susceptibility variants in genes encoding immune regulatory molecules, including IRF5, STAT4, BLK and TNFAIP3, many of which are shared across autoimmune diseases (Khatri *et al.,* 2022). Epigenetic mechanisms including aberrant DNA methylation and histone modification patterns in T and B lymphocytes further modulate gene expression, amplifying autoimmune responses in susceptible individuals (Lai *et al.,* 2025). Viral triggers, particularly Epstein-Barr virus, have been implicated in initiating loss of self-tolerance through molecular mimicry between viral antigens and salivary gland epithelial proteins (Morawiec *et al.,* 2025). Understanding the interplay between genetic predisposition, epigenetic regulation and environmental triggers is critical for developing targeted prophylactic and therapeutic strategies against Sjögren's syndrome.

A significant advance has been made in understanding the underlying mechanisms of Sjögren's syndrome; however, gaps remain in knowledge of specific genetic and molecular mechanisms that trigger and drive the disease. Identifying the key genes and pathways is essential in order to develop treatments that effectively target the underlying pathology. DisGeNET is a comprehensive database of genes linked to human diseases, which enables analysis of disease-specific genetic patterns and potential drug targets (Hu *et al.,* 2025). In this study, the top 30 Sjögren's syndrome-associated genes in DisGeNET were examined to explore relevant biological pathways, cellular components and molecular functions. Comprehensive enrichment analyses were conducted with Gene Ontology (GO), WikiPathways, Jensen databases, ChEA, HMDB metabolites and DrugMatrix to elucidate the complex interplay of genetic and molecular factors in Sjögren's syndrome and identify potential therapeutic targets.

Integration of multiple enrichment frameworks is particularly powerful for autoimmune disease research, as it enables simultaneous interrogation of gene set across biological processes, cellular compartments, molecular functions, regulatory networks and metabolic pathways. This layered approach minimizes the risk of missing biologically relevant associations that might only become apparent through one analytical lens while remaining invisible to others. Furthermore, the use of tissue-specific expression databases permits identification of the anatomical sites where disease-associated genes are preferentially active, providing spatial context that is directly relevant to the clinical phenotype. Together, these complementary analytical perspectives generate a systems-level understanding of Sjögren's syndrome molecular pathology that can prioritize candidate genes and pathways for subsequent experimental validation.

Materials and Methods

Gene selection and database usage: A systematic approach was followed to identify and analyze genes associated with Sjögren's syndrome. DisGeNET (Piñero *et al.,* 2020), a comprehensive database that brings together curated and text-mined gene-disease associations and serve as a primary source.

Top 30 genes with the strongest evidence for association with Sjögren's syndrome were selected based on DisGeNET's gene-disease association score, which considers publication support, experimental evidence strength, and consistency across data sources.

Gene Ontology and Pathway Analysis: Enrichr was used to perform the pathway and ontology analysis for the input gene list. This retrieved the enriched pathways and ontology terms. The terms with p-value < 0.05 were considered to be statistically significant.

Tissue, Subcellular and Transcription Factor Analysis: The Jensen_TISSUES and Jensen_COMPARTMENTS databases were used to assess tissue specificity and subcellular localization. ChEA_2022 analysis identified transcription factors that regulate multiple genes in the gene set, pointing to potential master regulators of Sjögren's syndrome gene expression.

Metabolite and Drug Associations: The HMDB_Metabolites and DrugMatrix databases were searched to explore the correlation of metabolites and the interaction of drugs with Sjögren's syndrome-related genes (Wishart *et al.,* 2022). This gave an insight into disease mechanisms, therapeutic targets, and whether existing drugs might be repurposed.

Data Visualization and Statistical Analysis: Enrichment results were visualized using bar plots (showing −log10 adjusted p-values) and detailed tables summarizing pathways, metabolites, drug associations, statistical measures and associated genes. Overlaps, odds ratios, and combined scores were documented to put the findings in context.

Computational tools and environment: All analyses were performed in R version 4.4.2, providing a robust platform for data handling, statistical analysis and visualization. Specific R packages were employed for gene set enrichment, pathway analysis and graphical representation, with package versions documented to ensure reproducibility.

Results and Discussion

A significant enrichment in immune-related biological processes was found on analyzing top 30 genes associated with Sjogrens syndrome, which highlights the central dysregulated immunity to the disease. The Gene Ontology biological process analysis revealed involvement in cytokine-mediated signaling, immune regulation, and inflammatory responses, consistent with the clinical hallmark of lymphocytic infiltration into exocrine glands and consequent glandular dysfunction (Fig. 1).

Among the enriched biological processes, cytokine-mediated signaling represented the dominant functional category, with IL-10, IL-6, IFNG and TNF collectively accounting for multiple top-ranked terms. The dual enrichment of pro-inflammatory mediators such as IFNG and TNF alongside the anti-inflammatory regulator IL-10 reflects the immunological imbalance that characterizes active Sjögren's syndrome, where regulatory circuits are overwhelmed by persistent inflammatory drive (Song *et al.,* 2024). Negative regulation of cytokine production was also significantly enriched, indicating that the gene set encodes not only effector cytokines but also their regulatory counterparts, consistent with the homeostatic feedback mechanisms that attempt to limit tissue damage (Al-atiyah *et al.,* 2026). The enrichment of response to lipopolysaccharide and bacterial molecular patterns suggests activation of innate immune pathways, raising the possibility that microbial dysbiosis in the oral and gut microbiome may contribute to the chronic immune activation observed in Sjögren's syndrome patients (Yang *et al.,* 2026). Regulation of smooth muscle cell proliferation was an unexpected enriched term, potentially reflecting the vascular and fibrotic consequences of sustained cytokine-driven inflammation in glandular and extraglandular tissues (Parisis *et al.,* 2020).

The transcriptomic basis of these enriched biological processes has been corroborated by independent expression profiling studies in minor salivary gland biopsies from Sjögren's syndrome patients (Pontarini *et al.,* 2025). Type I and type II interferon response genes are consistently overexpressed in affected glandular tissue, mirroring the interferon pathway enrichment identified in this bioinformatic analysis (Lee and Ashkar, 2018). The concordance between database-derived gene-disease associations and tissue-level transcriptomic data strengthens confidence in the biological relevance of the identified gene set. Moreover, the enrichment of genes involved in smooth muscle regulation and vascular responses is consistent with the vasculitis and peripheral neuropathy that complicate Sjögren's syndrome in a subset of patients with systemic disease, suggesting that vascular inflammation is an integral component of the broader molecular phenotype beyond glandular involvement (Mihai *et al.,* 2023).The cellular component analysis revealed that these genes predominantly encode secretoryproteins localizing to extracellular spaces and immune-related compartments, indicating that cytokines and signaling molecules are central drivers of immune and inflammatory responses. Their overrepresentation at immunological synapses and on cell surfaces further emphasizes their importance in activating immune cells and enabling intercellular communication (Fig. 2).

The enrichment of gene products within clathrin-coated endocytic vesicles and endoplasmic reticulum lumen compartments has particular mechanistic relevance to Sjögren's syndrome pathogenesis. Clathrin-mediated endocytosis is a critical route for the internalization and processing of extracellular antigens, a step that precedes MHC class II-mediated antigen presentation to $Cd4^{+}$ T helper cells. The localization of Sjögren's syndrome-associated proteins within MHC class II protein complexes directly implicates adaptive immune antigen presentation as a core molecular event in disease initiation and perpetuation (Masaki *et al.,* 2020). Endoplasmic reticulum stress, associated with the ER lumen-enriched proteins, may trigger

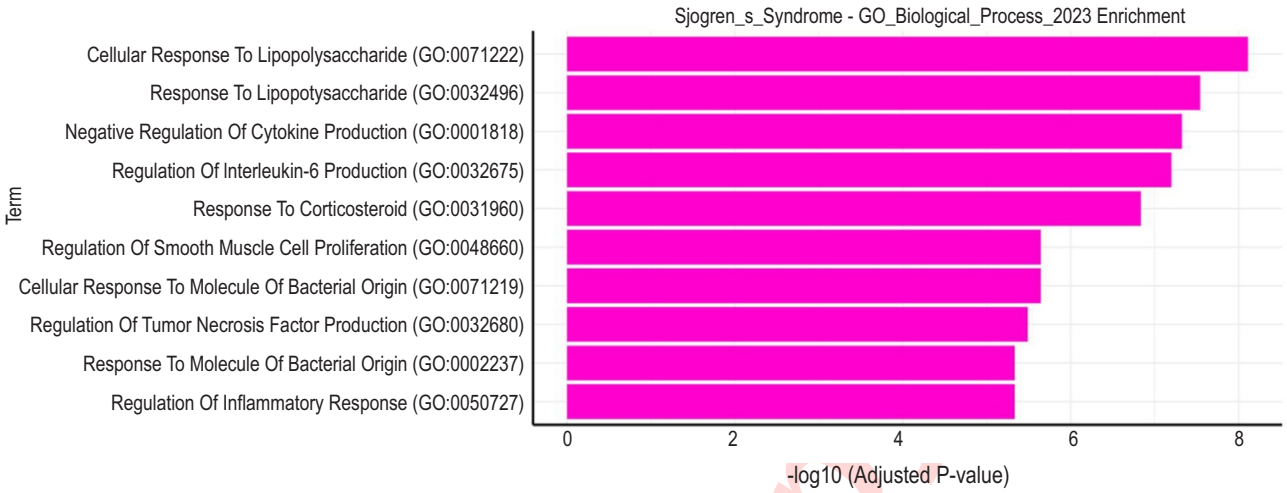


Fig. 1: GO_Biological_Process_2023 enrichment showing −log10 (Adjusted p-value ≤ 0.05) versus terms arranged sequentially.

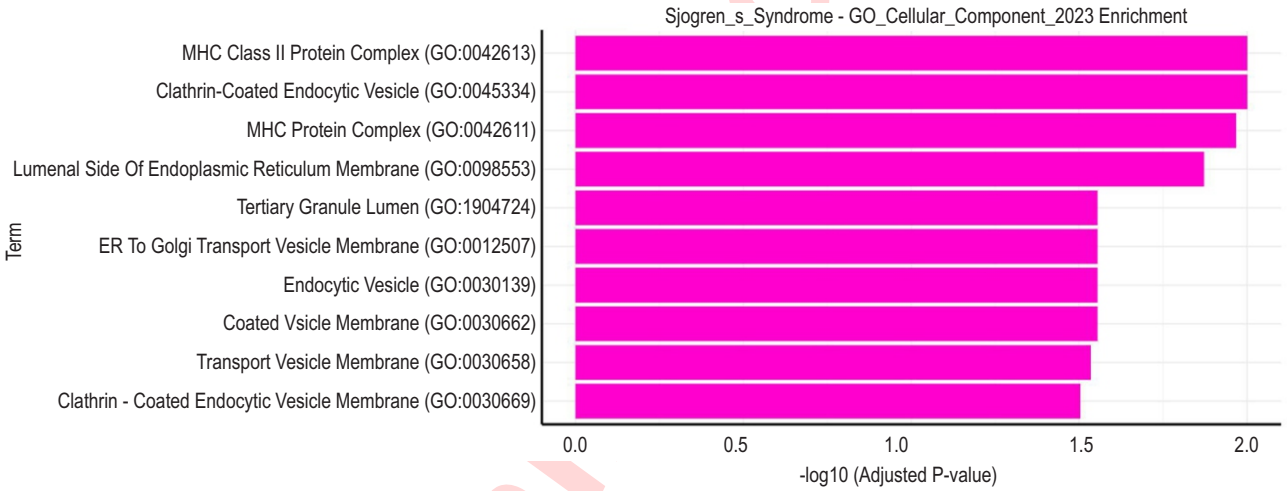


Fig. 2: GO_Cellular_Component_2023 enrichment showing −log10 (Adjusted p-value ≤ 0.05) versus terms arranged sequentially.

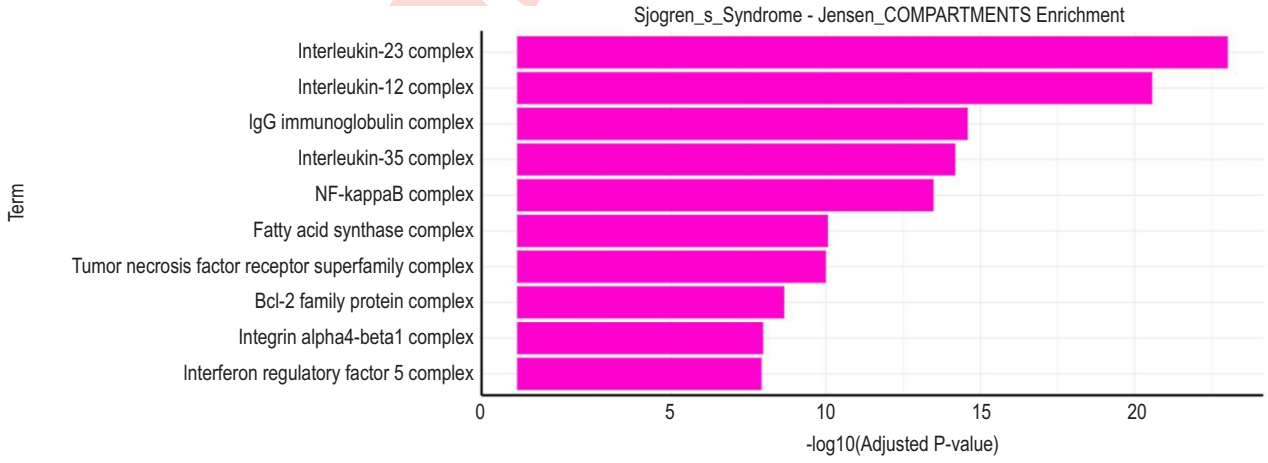


Fig. 3: Bar graph showing Jensen_COMPARTMENTS enrichment mapping −log10 (Adjusted p-value ≤ 0.05) against terms.

unfolded protein response pathways that amplify inflammatory cytokine production in acinar epithelial cells. The enrichment of tertiary granule lumen and transport vesicle membrane terms suggests that Sjögren's syndrome-associated proteins participate in regulated secretion pathways, potentially disrupting the normal secretory function of salivary and lacrimal gland epithelial cells (Kusampudi *et al.,* 2025). The MHC class II protein complex enrichment identified in this analysis carries direct clinical relevance, as HLA-DR and HLA-DQ alleles confer the strongest known genetic risk for Sjögren's syndrome susceptibility (Thorlacius *et al.,* 2023). Proteins enriched within MHC class II complexes facilitate the presentation of autoantigenic peptides derived from Ro60 and La antigens to autoreactive $Cd4^{+}$ T cells, a central event in the breakdown of self-tolerance in Sjögren's syndrome (Ishina *et al.,* 2023). The identification of gene products enriched within secretory granule compartments suggests disruption of regulated exocytosis in acinar cells, a mechanism that may directly impair salivary and lacrimal gland secretion and contribute to the cardinal symptoms of xerostomia and xerophthalmia (Wu *et al.,* 2023).

The molecular function analysis revealed enrichment for cytokine activity and receptor binding, supporting the concept that dysregulated cytokine signaling contributes to the onset and progress of disease. Highly enriched pathways (Agrawal *et al.,* 2024) were identified which included allograft rejection (WP2328) and proinflammatory and profibrotic mediators (WP5095), implicating T-cell activation, HLA-mediated antigen presentation, and tissue inflammation as central mechanisms. Other enriched pathways included immune infiltration in pancreatic cancer, T-cell activation in SARS-CoV-2 infection, and cytokine-cytokine receptor interaction, demonstrating shared molecular features with other immune-mediated conditions. The enrichment of proinflammatory and profibrotic mediator pathways warrants particular attention in the context of Sjögren's syndrome-associated organ damage. Progressive fibrosis of salivary and lacrimal glands is a recognized consequence of sustained lymphocytic infiltration and cytokine-driven tissue remodeling, contributing to the irreversible loss of secretory function (Ma *et al.,* 2024). The identification of profibrotic pathway genes among the top Sjögren's syndrome-associated genes provides molecular support for investigating anti-fibrotic agents as complementary therapies alongside conventional immuno-suppressive strategies. The overlap with cytokine-cytokine receptor interaction pathways reflects the extensive intercellular signaling network that coordinates immune cell recruitment, activation, and effector function within the inflamed gland (Żurawek *et al.,* 2025).

The transcription factor analysis identifying interferon regulatory factors (IRFs) as master regulators of the identified gene set is consistent with the well-established interferon signature that serves as a defining molecular feature of Sjögren's syndrome and a potential target for type I interferon receptor blockade (Wang *et al.,* 2024). The connection between Sjögren's syndrome-associated genes and T-cell activation in SARS-CoV-2 infection pathways reflects the broader concept of immune cross-reactivity between viral triggers and self-antigens (Maslinska and Kostyra-Grabczak, 2022). Clinical observations of de novo Sjögren's syndrome diagnosis following COVID-19 infection have been reported, and the shared molecular pathways identified in this analysis provide mechanistic support for these clinical observations. The cytokine-cytokine receptor interaction pathway enrichment encompasses a broad network of ligand-receptor pairs including IL-10/IL-10R, IFNγ/IFNGR, and TNF/TNFR axes, all of which represent established or emerging drug targets in autoimmune disease management. Blockade of specific cytokine-receptor interactions using monoclonal antibodies or small molecule antagonists could selectively attenuate pathogenic signaling while preserving protective immune functions. Spatial analyses using Jensen COMPARTMENTS (Fig. 3) and TISSUES revealed specific subcellular and tissue localization of the identified gene products, especially in moisture-producing glands, provides insight into the autoimmune responses to target specific tissue compartments.

The tissue expression profiling results confirm that Sjögren's syndrome-associated genes are not uniformly expressed across body tissues, but show preferential enrichment in immune and glandular compartments. The enrichment in salivary gland-related tissues directly validates the clinical relevance of the identified gene set, as these are the primary target organs of the autoimmune attack in Sjögren's syndrome (Qi *et al.,* 2024). Detection of significant expression in lymphoid tissues, including lymph nodes and spleen, is consistent with the systemic immune activation that underlies both glandular and extraglandular manifestations. Notably, the enrichment of gene expression in tissues beyond the classical exocrine compartments supports the concept of Sjögren's syndrome as a systemic autoimmune disease with broad tissue involvement (Mihai *et al.,* 2023). These findings have direct implications for the design of targeted therapies, suggesting that interventions delivered systemically rather than locally may be necessary to address the full spectrum of disease manifestations.

The NADPH pathway enrichment identified in the metabolite interaction analysis points toward oxidative stress as an underappreciated contributor to Sjögren's syndrome pathobiology (Suffiotti *et al.,* 2026). Reactive oxygen species generated through NADPH oxidase activity are known to exacerbate epithelial cell apoptosis, trigger danger signal release, and amplify innate immune activation in autoimmune glandular disease (Taylor and Tse, 2021). Furthermore, oxidative modification of self-antigens such as Ro60 and La can enhance their immunogenicity, potentially lowering the threshold for autoreactive B and T cell activation. Antioxidant strategies, including N-acetylcysteine supplementation and pharmacological NADPH oxidase inhibitors, therefore represent a rational complement to cytokine-targeted therapies in Sjögren's syndrome, particularly in patients with elevated oxidative stress biomarkers (Lin *et al.,* 2021). Future metabolomic profiling of patient serum and minor salivary gland tissue will be essential to confirm the clinical significance of the metabolite associations

Table 1: HMDB_Metabolites including the columns: terms, overlap, p value, adjusted p value, Old p value, Odds Ratio, Combined Score and Genes

Term	Overlap	P. value	Adjusted. P. value	Odds. Ratio	Combined. Score	Genes
Simvastatin (HMDB05007)	4/25	p<0.05	0.000002391605	146.146520	2,454.33987	*IL6;IFNG;TNF;MMP9*
Butyric acid (HMDB00039)	1/11	p<0.05	0.062073606443	68.827586	282.99490	*TNF*
Atorvastatin (HMDB05006)	1/17	p<0.05	0.062073606443	43.004310	158.28469	*TNF*
NADPH (HMDB00221)	2/174	p<0.05	0.062073606443	8.221761	29.42357	*NCF1;CYP1A1*
1,4-Naphthalenedione, 2-methyl- (HMDB01892)	1/20	p<0.05	0.062073606443	36.208711	127.46621	*CYP1A1*

Table 2: DrugMatrix is represented with columns detailing terms, overlap, p value, adjusted p value, Old p value, Odds Ratio, Combined Score and Genes

Term	Overlap	P. value	Adjusted. P. value	Odds. Ratio	Combined. Score	Genes
Busulfan-3 mg/kg in Corn Oil-Rat-Bone marrow-0.25d-up	6/302	p<0.05	0.006948117	16.61655	203.0391	*SSB;TNIP1;VIM;CCR5; TNF;MMP9*
Chlorambucil-4.5 mg/kg in Corn Oil-Rat-Bone marrow-3d-up	6/306	p<0.05	0.006948117	16.39167	199.0543	*SSB;CYP1A1;VIM;*
CCR5;TNF;MMP9Cytarabine-487 mg/kg in Saline-Rat-Bone marrow-5d-dn	5/293	p<0.05	0.028030162	13.66806	130.9952	*CYP1A1;VIM;CCR5; TNF;MMP9*
Leucovorin-1500 mg/kg in CMC-Rat-Bone marrow-3d-dn	5/301	p<0.05	0.028030162	13.29324	125.7116	*SSB;TNIP1;VIM; TNF;MMP9*
Thioguanine-12 mg/kg in Corn Oil-Rat-Bone marrow-3d-up	5/309	p<0.05	0.028030162	12.93816	120.7538	*CYP1A1;VIM;CCR5; TNF;MMP9*

identified in this computational analysis.

Transcription factor analysis (ChEA 2022) identified key regulators of these genes. The metabolite (Table 1) and drug association (Table 2) analyses highlighted connections with simvastatin, other metabolites and chemotherapy agents, suggesting potential metabolic and therapeutic relevance. Overall, these findings provide molecular insights into disease mechanisms and potential avenues for intervention in Sjögren's syndrome. The identification of NF-κB and STAT family members among the transcription factors regulating Sjögren's syndrome-associated genes is particularly significant from a therapeutic standpoint. NF-κB signaling coordinates the expression of numerous pro-inflammatory cytokines including IL-6, TNF, and IL-1β, and its persistent activation in lymphocytes and epithelial cells is a hallmark of Sjögren's syndrome pathobiology (Sisto *et al.,* 2020). STAT3, downstream of IL-6 and IL-10 signaling, regulates both pro-inflammatory Th17 differentiation and anti-inflammatory regulatory T-cell function, placing it at a critical immunological crossroads. Pharmacological targeting of these transcription factors, through JAK inhibitors or NF-κB pathway modulators, represents an area of active investigation in Sjögren's syndrome clinical trials (Woś and Tabarkiewicz, 2021). The drug association analysis further highlighted chemotherapy agents including busulfan and chlorambucil as having gene expression profiles overlapping with Sjögren's syndrome, reflecting the shared lymphocyte-targeted mechanisms between cytotoxic therapy and autoimmune suppression. The metabolite associations, particularly with simvastatin, suggest there is crosstalk between lipid metabolism and inflammation through IL6, IFNG, TNF and MMP9, which indicates simvastatin might have immunomodulatory benefits (Harikrishnan *et al.,* 2025).

The systematic analysis of 30 most prominent Sjögren's syndrome-associated genes provides strong insights into the molecular basis of this complex autoimmune disease, showing how dysregulated immunity, inflammation, and disrupted cellular pathways all play a role. Immune-related biological processes were overrepresented, which emphasizes how pivotal cytokine-mediated signaling is. Major cytokines like IL10, IL6, IFNG, TNF, and IL17A coordinate immune mechanisms in Sjögren's syndrome, and when the balance between pro- and anti-inflammatory mediators gets disrupted, it can drive persistent inflammation and tissue damage. The biological process enrichment results collectively delineate an immune activation program characterized by cytokine overproduction, impaired immune regulation, and persistent inflammatory signaling. This molecular portrait aligns with the clinical reality of Sjögren's syndrome, where patients experience fluctuating disease activity driven by cycles of immune activation and incomplete resolution. The enrichment of both activating and regulatory cytokine pathways within the same gene set highlights the dynamic tension between pathogenic and protective immune forces in this disease. Identifying the molecular tipping points that shift this balance

towards chronic inflammation is essential for designing interventions that restore immune homeostasis without inducing global immunosuppression and the associated risks of opportunistic infection. The enrichment of allograft rejection pathways demonstrate shared mechanisms between transplant rejection and Sjögren's syndrome, involving HLA-mediated antigen presentation and T-cell activation. This supports the concept that molecular mimicry may trigger autoimmunity. Cellular component analysis revealed widespread localization of SS-related gene products to extracellular spaces and immune compartments, consistent with lymphocytic infiltration of exocrine glands.

The metabolite and drug association results carry direct translational implications. Simvastatin's interaction with IL6, IFNG, TNF, and MMP9 — all central mediators in Sjögren's syndrome — supports the biological plausibility of statin repurposing as an immunomodulatory adjunct therapy. Statins are known to downregulate MHC class II expression, suppress T-cell activation, and inhibit NF-κB-driven cytokine transcription, mechanisms directly relevant to curtailing the autoimmune attack on exocrine glands. Prospective clinical trials examining statin use in Sjögren's syndrome patients with elevated inflammatory markers are warranted based on these computational findings. The association of NADPH and its metabolic network with Sjögren's syndrome genes further implicates oxidative stress pathways in disease pathophysiology, suggesting that antioxidant strategies may complement anti-inflammatory approaches in a multimodal treatment framework. Validation of these metabolite-gene interactions in patient-derived cellular models and clinical biomarker studies should be prioritized in future research.

Several limitations of this study merit consideration. The analysis relies on secondary gene-disease association data from DisGeNET, which may not capture all genetic contributors to Sjögren's syndrome, particularly rare variants and gene-gene interactions not yet reported in the literature. The restriction to the top 30 associated genes, while justified by the need for statistical stringency, inevitably excludes additional relevant candidates that may have moderate, but biologically meaningful associations. The enrichment findings are entirely computational and require prospective experimental validation in patient-derived primary cells, organoid models, and well-characterized clinical cohorts. Furthermore, enrichment analysis results reflect population-level gene-disease associations and may not capture the heterogeneity of molecular mechanisms across individual patients, who may differ substantially in their underlying immunological drivers. Future studies incorporating multi-omics data from longitudinal patient cohorts, including transcriptomic, proteomic, and epigenomic profiles, will be essential to translate these computational observations into actionable clinical insights and validated therapeutic targets. The present findings nonetheless establish a robust computational foundation for mechanistically grounded hypothesis generation in Sjögren's syndrome research.

In conclusion, the comprehensive bioinformatic profiling of the top 30 Sjögren's syndrome-associated genes has yielded an integrative molecular map of the immunological and inflammatory processes underlying this complex autoimmune disease. The convergent enrichment of cytokine signaling, immune receptor biology, extracellular secretory compartments, and transcription factor regulatory networks paints a coherent picture of how dysregulated immune activation drives progressive exocrine gland destruction. Key cytokines including IL-10, IL-6, IFNG, and TNF emerge as central molecular nodes that simultaneously drive pathogenic inflammation and represent tractable therapeutic targets. The metabolite and drug association data further highlight the potential for repurposing existing agents, particularly statins, to modulate the inflammatory milieu of Sjögren's syndrome. These findings provide a prioritized set of molecular targets and testable hypotheses that can guide experimental and clinical research aimed at improving diagnostic precision and therapeutic outcomes for patients with this debilitating autoimmune condition.

Acknowledgment

Authors thank the Central Research Laboratory for Molecular Genetics, Bioinformatics and Machine Learning at Apollo Institute of Medical Sciences and Research Chittoor Murukambattu-517127, Andhra Pradesh, India for the infrastructure.

Authors' contribution: A. Dharaneedhar, K.M. Jyothi, E.V. Ravikanth, G.M. Chowdary and U. Adiga: All contributed equally to the study's design, data acquisition, analysis, and manuscript preparation.

Funding: Not applicable.

Research content: The research content of manuscript is original and has not been published elsewhere.

Ethical approval: Not applicable.

Conflict of interest: The authors declare that there is no conflict of interest.

Data availability: Not applicable.

Consent to publish: All authors agree to publish the paper in *Journal of Environmental Biology.*

References

Agrawal, A., H. Balcı, K. Hanspers, S.L. Coort, M. Martens, D.N. Slenter, F. Ehrhart, D. Digles, A. Waagmeester, I. Wassink, T. Abbassi-Daloii, E.N. Lopes, A. Iyer, J.M. Acosta, L.G. Willighagen, K. Nishida, A. Riutta, H. Basaric, C.T. Evelo, E.L. Willighagen, M. Kutmon and A.R. Pico: WikiPathways 2024: Next generation pathway database. *Nucl. Acids Res.,* **52**, D679-D689 (2024).

Al-atiyah, R., N.D. Verma, G.T. Tran, S.J. Hodgkinson and B.M. Hall: Cytokines associated with activation of CD4+CD25+Foxp3+ T regulatory cells. *Int. J. Mol. Sci.,* **27**, 2085 (2026).

Bowman, S.J.: Sjogren's disease-aspects of clinical disease beyond dry eyes/mouth. *J. Clin. Med.,* **15**, 1189 (2026).

Diggins, E.C. and M.L. Weller: Hormonal transitions across the lifespan shape susceptibility to Sjogren's disease. *Rheumatology,* **65**, keag087 (2026).

Harikrishnan, N., R.K. Nesamani, S.A. Sherin, K. Sanjeev and M. Sekar: Effect of simvastatin on expression of interleukins 6 and 10 and matrix metalloproteinase: 9 when used as an intracanal medicament in teeth with symptomatic apical periodontitis-a triple blind randomized controlled trial. *J. Transl. Med.,* **23**, 760 (2025).

Hu, Y., X. Guo, Y. Yun, L. Lu, X. Huang and S. Jia: DisGeNet: A disease-centric interaction database among diseases and various associated genes. *Database,* **2025**, baae122 (2025).

Hu, Y., B. Wen, Y. Zhang, X. Wang, X. Duan, H. Li, Y. Fan, H. Shang and Y. Jing: Sjögren's syndrome: Epidemiology, classification criteria, molecular pathogenesis, diagnosis, and treatment. *MedComm,* **6**, e70297 (2025).

Ishina, I.A., M.Y. Zakharova, I.N. Kurbatskaia, A.E. Mamedov, A.A. Belogurov and A.G. Gabibov: MHC class II presentation in autoimmunity. *Cells,* **12**, 314 (2023).

Jin, L., M. Dai, C. Li, J. Wang and B. Wu: Risk factors for primary Sjögren's syndrome: A systematic review and meta-analysis. *Clin. Rheumatol.,* **42**, 327-338 (2023).

Khatri, B., K.L. Tessneer, A. Rasmussen, F. Aghakhanian, T.R. Reksten, A. Adler, I. Alevizos, J.M. Anaya, L.A. Aqrawi, E. Baecklund, J.G. Brun, S.M. Bucher, M.L. Eloranta, F. Engelke, H. Forsblad-d'Elia, S.B. Glenn, D. Hammenfors, J. Imgenberg-Kreuz, J.L. Jensen, S.J.A. Johnsen, M.V. Jonsson, M. Kvarnström, J.A. Kelly, H. Li, T. Mandl, J. Martín, G. Nocturne, K.B. Norheim, Ø. Palm, K. Skarstein, A.M. Stolarczyk, K.E. Taylor, M. Teruel, E. Theander, S. Venuturupalli, D.J. Wallace, K.M. Grundahl, K.S. Hefner, L. Radfar, D.M. Lewis, D.U. Stone, C.E. Kaufman, M.T. Brennan, J.M. Guthridge, J.A. James, R.H. Scofield, P.M. Gaffney, L.A. Criswell, R. Jonsson, P. Eriksson, S.J. Bowman, R. Omdal, L. Rönnblom, B. Warner, M. Rischmueller, T. Witte, A.D. Farris, X. Mariette, M.E. Alarcon-Riquelme, C.H. Shiboski, M. Wahren-Herlenius, W.F. Ng, K.L. Sivils, I. Adrianto, G. Nordmark and C.J. Lessard: Genome-wide association study identifies Sjögren's risk loci with functional implications in immune and glandular cells. *Nat. Commun.,* **13**, 4287 (2022).

Kusampudi, S., V. Meganathan and V. Boggaram: Endoplasmic reticulum stress and unfolded protein response sensor ERN1 regulates organic dust induction of lung inflammation. *FASEB BioAdv.,* **7**, e70031 (2025).

Lai, X., J. Huang, H. Li, C. Chang, R. Li, X. Li, X. Yan and L. Dong: Epigenetic regulatory mechanisms of autoimmune skin diseases: Novel biomarkers and therapeutic prospects. *Clin. Epigenetics,* **17**, 182 (2025).

Lee, A.J. and A.A. Ashkar: The dual nature of type I and type II interferons. *Front. Immunol.,* **9**, 2061 (2018).

Lin, W., P. Shen, Y. Song, Y. Huang and S. Tu: Reactive oxygen species in autoimmune cells: Function, differentiation, and metabolism. *Front. Immunol.,* **12**, 635021 (2021).

Ma, D., Y. Feng and X. Lin: Immune and non-immune mediators in the fibrosis pathogenesis of salivary gland in Sjögren's syndrome. *Front. Immunol.,* **15**, 1421436 (2024).

Mallick, H., V. Karri and S. Dalia: Non-gastric mucosa-associated lymphoid tissue lymphomas: A narrative review of pathogenesis, diagnosis, and treatment strategies. *Ann. Transl. Med.,* **13**, 78 (2025).

Masaki, K., Y. Hiraki, H. Onishi, Y. Satoh, P.A. Roche, S. Tanaka and K. Furuta: Ligation of MHC class II induces PKC-dependent clathrin-mediated endocytosis of MHC class II. *Cells,* **9**, 1810 (2020).

Maslinska, M. and K. Kostyra-Grabczak: The role of virus infections in Sjögren's syndrome. *Front. Immunol.,* **13**, 823659 (2022).

Mihaescu, G., G.G. Pircalabioru, C.N. Roznovan, L.M. Ditu, M.M. Comanici and O. Savu: Interferons in autoimmunity: From loss of tolerance to chronic inflammation. *Biomedicines,* **13**, 2472 (2025).

Mihai, A., C. Caruntu, C. Jurcut, F.C. Blajut, M. Casian, D. Opris-Belinski, R. Ionescu and A. Caruntu: The spectrum of extraglandular manifestations in primary Sjögren's syndrome. *J. Pers. Med.,* **13**, 961 (2023).

Morawiec, N., B. Adamczyk, A. Spyra, M. Herba, S. Boczek, N. Korbel, P. Polechoński and M. Adamczyk-Sowa: The role of Epstein-Barr virus in the pathogenesis of autoimmune diseases. *Medicina,* **61**, 1148 (2025).

Negrini, S., G. Emmi, M. Greco, M. Borro, F. Sardanelli, G. Murdaca, F. Indiveri and F. Puppo: Sjögren's syndrome: A systemic autoimmune disease. *Clin. Exp. Med.,* **22**, 9-25 (2022).

Parisis, D., C. Chivasso, J. Perret, M.S. Soyfoo and C. Delporte: Current state of knowledge on primary Sjögren's syndrome, an autoimmune exocrinopathy. *J. Clin. Med.,* **9**, 2299 (2020).

Piñero, J., J.M. Ramírez-Anguita, J. Saüch-Pitarch, F. Ronzano, E. Centeno, F. Sanz and L.I. Furlong: The DisGeNET knowledge platform for disease genomics: 2019 update. *Nucl. Acids Res.,* **48**, D845-D855 (2020).

Pontarini, E., D. Lucchesi, E. Sciacca, G. Cavallaro, Q. Song, D. Galbraith, E. Thomas, A. Marino, N. Sutcliffe, A.R. Tappuni, R. Giacomelli, A. Pulvirenti, S.J. Bowman, L.Y. Hao, K. Sivils, C. Pitzalis, M.J. Lewis and M. Bombardieri: Transcriptomic profiling of Sjögren's disease salivary glands identifies signatures associated with both follicular and extrafollicular responses linked to rheumatoid factor and anti-La/SSB seropositivity. *Ann. Rheum. Dis.,* **84**, 1822-1835 (2025).

Qi, W., J. Tian, G. Wang, Y. Yan, T. Wang, Y. Wei, Z. Wang, G. Zhang, Y. Zhang and J. Wang: Advances in cellular and molecular pathways of salivary gland damage in Sjögren's syndrome. *Front. Immunol.,* **15**, 1405126 (2024).

Sisto, M., D. Ribatti and S. Lisi: Understanding the complexity of Sjögren's syndrome: Remarkable progress in elucidating NF-κB mechanisms. *J. Clin. Med.,* **9**, 2821 (2020).

Song, Y., J. Li and Y. Wu: Evolving understanding of autoimmune mechanisms and new therapeutic strategies of autoimmune disorders. *Signal Transduct. Target. Ther.,* **9**, 263 (2024).

Soyfoo, M.S. and C. Nicaise: Pathophysiologic role of interleukin-33/ST2 in Sjögren's syndrome. *Autoimmun. Rev.,* **20**, 102756 (2021).

Suffiotti, M., L. Tanner, L. Kozera, A. Sebastian, A. van Maurik and D. Strasser: Sjögren's disease metabolome reveals biomarker signatures to characterise patients and assess disease activity. *RMD Open,* **12**, 006312 (2026).

Taylor, J.P. and H.M. Tse: The role of NADPH oxidases in infectious and inflammatory diseases. *Redox Biol.,* **48**, 102159 (2021).

Thorlacius, G.E., A. Björk and M. Wahren-Herlenius: Genetics and epigenetics of primary Sjögren syndrome: Implications for future therapies. *Nat. Rev. Rheumatol.,* **19**, 288-306 (2023).

Tian, Y., H. Yang, N. Liu, Y. Li and J. Chen: Advances in pathogenesis of Sjögren's syndrome. *J. Immunol. Res.,* **2021**, 5928232 (2021).

Wang, L., Y. Zhu, N. Zhang, Y. Xian, Y. Tang, J. Ye, F. Reza, G. He, X. Wen and X. Jiang: The multiple roles of interferon regulatory factor family in health and disease. *Signal Transduct. Target. Ther.,* **9**, 282 (2024).

Wishart, D.S., A. Guo, E. Oler, F. Wang, A. Anjum, H. Peters, R. Dizon, Z. Sayeeda, S. Tian, B.L. Lee, M. Berjanskii, R. Mah, M. Yamamoto, J. Jovel, C. Torres-Calzada, M. Hiebert-Giesbrecht, V.W. Lui, D.

Varshavi, D. Varshavi, D. Allen, D. Arndt, N. Khetarpal, A. Sivakumaran, K. Harford, S. Sanford, K. Yee, X. Cao, Z. Budinski, J. Liigand, L. Zhang, J. Zheng, R. Mandal, N. Karu, M. Dambrova, H.B. Schiöth, R. Greiner and V. Gautam: HMDB 5.0: The human metabolome database for 2022. *Nucl. Acids Res.,* **50**, D622-D631 (2022).

Woś, I. and J. Tabarkiewicz: Effect of interleukin-6, -17, -21, -22, and -23 and STAT3 on signal transduction pathways and their inhibition in autoimmune arthritis. *Immunol. Res.,* **69**, 26-42 (2021).

Wu, K.Y., M. Kulbay, C. Tanasescu, B. Jiao, B.H. Nguyen and S.D. Tran: An overview of the dry eye disease in Sjögren's syndrome using our current molecular understanding. *Int. J. Mol. Sci.,* **24**, 1580 (2023).

Yang, Y., G. Wang, Y. Song, J. Ma and A. Liu: Immunomodulatory effects of oral microbiota in the pathogenesis of rheumatoid arthritis. *Front. Immunol.,* **17**, 1707949 (2026).

Zhao, T., R. Zhang, Z. Li, D. Qin and X. Wang: A comprehensive review of Sjögren's syndrome: Classification criteria, risk factors, and signaling pathways. *Heliyon,* **10**, e36220 (2024).

Żurawek, M., I. Ziółkowska-Suchanek and K. Iżykowska: Fibrosis in immune-mediated and autoimmune disorders. *J. Clin. Med.,* **14**, 6636 (2025).