Journal of Science Research International (JSRI)
ISSN: 2456-6365 (Online)

OPEN ACCESS

NETWORK BASED ANALYSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ASSOCIATED GENES USING WEB BASED BIOINFORMATICS TOOLS

Meenakshi Johri*, Bindu Rajaguru and Aditi Malandkar

Department of Biotechnology,

Pillai College of Arts, Commerce & Science (Empowered Autonomous), New Panvel, India

**Corresponding author E-mail: m.johri101@gmail.com*

ORCID iD: 0009-0002-0404-3473

Received: 27 January 2026	Revised: 26 February 2026	Accepted: 15 March 2026	Published: 30 March 2026

DOI: **https://doi.org/10.5281/zenodo.19469043**

Abstract:

Systemic Lupus Erythematosus (SLE) is a long-term autoimmune disease in which the immune system mistakenly attacks the body's own tissues. This leads to the production of harmful autoantibodies and immune complexes that cause inflammation and damage in multiple organs such as the skin, joints, kidneys, and blood cells. One of the main causes of SLE is an imbalance between the innate and adaptive immune systems. In this condition, B-cells and T-cells become abnormally activated, the body fails to properly clear dead cells, and there is persistent type I interferon signaling. These factors together contribute to continuous immune activation and tissue injury. The symptoms of SLE vary widely among patients. Common manifestations include fatigue, skin rashes, joint pain, and inflammation of body tissues, while severe cases may lead to organ-threatening complications such as lupus nephritis, which affects the kidneys and significantly increases long-term health risks. Diagnosis is based on a combination of clinical symptoms and laboratory tests, especially the presence of antinuclear antibodies (ANA) and other disease-specific markers. In treatment, hydroxychloroquine is commonly used as the first-line therapy because it helps reduce disease activity and improves survival. Depending on disease severity, additional immunosuppressive drugs and biologic therapies such as belimumab, anifrolumab, and voclosporin may also be used. Despite advances in research and treatment, SLE remains a complex and unpredictable disease, making personalized treatment strategies an ongoing challenge.

Keywords: *Systemic Lupus Erythematosus (SLE), Lupus Nephritis, Hub Genes, Disease–Gene Association, Protein–Protein Interaction Network.*

Introduction

Systemic lupus erythematosus (SLE) is a chronic, heterogeneous, multisystem autoimmune disorder characterized by dysregulated immune responses leading to inflammation and immune-mediated injury in multiple organs including the skin, joints, kidneys, hematologic systems, and central nervous system [1, 2]. The disease displays a wide spectrum of clinical manifestations ranging from mild symptoms such as fever, fatigue, and arthralgia to severe, life-threatening complications such as lupus nephritis, neuropsychiatric involvement, and cardiovascular disease [2, 3]. Because of its clinical heterogeneity and overlapping features with other disorders, SLE poses significant diagnostic and therapeutic challenges in clinical practice [1, 2].

Epidemiologically, SLE is a relatively uncommon condition but imposes significant morbidity and mortality worldwide. The disease exhibits marked sex bias, affecting females approximately nine times more frequently than males, with peak incidence during the reproductive years [6]. Geographic and ethnic differences in disease prevalence and severity have been observed, with individuals of African, Asian, and Hispanic ancestry demonstrating higher disease burden compared with individuals of European descent [4]. SLE affects millions of individuals globally, and although survival has improved significantly over the past several decades due to advances in diagnosis and treatment, patients still experience reduced life expectancy and quality of life due to disease activity and complications [5, 2].

The etiology of SLE is complex and multifactorial, involving the interplay of genetic predisposition, epigenetic factors, hormonal influences, and environmental triggers such as ultraviolet light, infections, drugs, and smoking [6, 1, 7]. Genome-wide association studies (GWAS) and candidate gene analyses have identified more than 40 genetic loci associated with SLE susceptibility, many of which regulate immunologic pathways including apoptosis, immune complex clearance, and cytokine production [8, 9]. In addition to genetic risk factors, environmental exposures and hormonal changes—particularly those related to estrogen—modulate immune function and contribute to the loss of tolerance that precipitates SLE onset and flares [6, 4, 10].

Central to the pathogenesis of SLE is the breakdown of immunological self-tolerance resulting in chronic activation of both the innate and adaptive immune systems. Dysregulated innate immunity includes defective clearance of apoptotic cells, abnormal activation of Toll-like receptors, and overproduction of pro-inflammatory cytokines including type I interferons, which together amplify inflammatory responses and autoimmunity [1, 10, 11]. Adaptive immune dysregulation involves aberrant B- and T-lymphocyte activity characterized by autoreactive B cell expansion, excessive autoantibody production, and impaired regulatory mechanisms [1, 11, 12]. These autoreactive antibodies, particularly antinuclear antibodies (ANA) and anti-double stranded DNA (anti-dsDNA) antibodies, form immune complexes that deposit in tissues and activate complement pathways, thereby perpetuating inflammation and organ damage [2, 13, 14]. The hallmark serological presence of ANA in over 95% of SLE patients underscores its importance in disease diagnosis and monitoring [13].

Lupus nephritis, a frequent and serious complication of SLE, illustrates the pathogenic consequences of immune complex deposition. Approximately 40–70% of SLE patients develop renal involvement during their disease course, and lupus nephritis is a leading cause of morbidity and long-term renal damage [15, 16]. Immune complexes deposited in glomeruli trigger inflammatory cascades involving complement activation, infiltration of immune cells, and cellular injury that ultimately led to proteinuria, impaired renal function, and in severe cases, end-stage renal disease [15, 16]. The multifaceted genetic, immunological, and environmental factors that

contribute to lupus nephritis demonstrate the complexity of SLE pathogenesis and the challenges in developing effective interventions.

Materials and Methods

Study area

The study area for this research is defined by an in silico computational framework. Data was harvested from global biocuration databases (DisGeNET, OMIM) and processed locally at Pillai College Of Arts Commerce and Science using a Lenovo idea pad 3 workstation. The 'biological site' under investigation is the human molecular interactome, specifically focusing on the regulatory networks associated with Systemic lupus erythematosus pathology.

Experimental design

This study used freely available bioinformatics tools to explore the molecular basis of systemic lupus erythematosus and to identify important genes and biological pathways that may serve as potential targets for drug discovery. Public databases and online analysis platforms were systematically used to collect, analyze, and interpret genetic information related to breast carcinoma. The workflow was carried out in a logical and sequential manner, beginning with disease gene identification and ending with pathway-level interpretation.

1. Identification of SLE-associated genes using DisGeNET

Systemic Lupus Erythematosus (SLE)–associated genes were identified using the DisGeNET database a comprehensive platform integrating gene–disease associations from curated repositories, GWAS studies, animal models, and scientific literature.

The disease term “Systemic Lupus Erythematosus” (UMLS CUI: C0024141) was queried in the Disease Browser. Gene–disease associations (GDAs) were retrieved along with DisGeNET score, evidence level, and source databases.

2. Protein–Protein Interaction (PPI) network construction using STRING

To understand functional interactions among the identified genes, a protein–protein interaction (PPI) network was constructed using the STRING

STRING generated a PPI network illustrating functional associations. Network parameters such as node degree, clustering coefficient, and interaction enrichment p-value were recorded. The network was exported for visualization and hub gene analysis.

3. Gene–gene interaction and functional prediction using GeneMANIA

To explore gene function and co-expression relationships, the gene list was analyzed using GeneMANIA this tool predicts gene function based on:

- Co-expression
- Physical interactions
- Genetic interactions
- Pathway co-membership
- Shared protein domains

The SLE gene set was submitted with default settings, and GeneMANIA generated an extended network including related genes. Functional enrichment provided insight into biological processes linked to immune response, cytokine signaling, and regulation of apoptosis.

4. Functional enrichment analysis using Enrichr

To determine biological significance, functional enrichment analysis was performed using Enrichr.

This analysis identified immune-related pathways, interferon signaling, cytokine-mediated pathways, and apoptotic mechanisms relevant to SLE pathogenesis.

5. Pathway Mapping and Analysis Using Reactome

To visualize disease-related molecular pathways, genes were further analyzed in the Reactome Pathway Database

These pathways were mapped to understand the molecular mechanisms underlying immune dysregulation in SLE.

6. Identification of potential therapeutic targets

Hub genes and highly enriched pathway genes were evaluated as potential therapeutic targets based on:

- Involvement in critical immune and inflammatory pathways
- Literature evidence linking them to SLE severity
- Drug-target information from databases such as DrugBank and published studies

Genes involved in type I interferon signaling, B-cell activation, cytokine production, and complement pathways were prioritized due to their established roles in SLE immunopathology and existing or emerging targeted therapies.

Sample collection

Through digital records of a total of 30 high-confidence genes were collected from DisGeNET, which aggregates clinical and experimental evidence of genotype-phenotype associations for Systemic lupus erythematosus.

1. Analytical procedures

i. Network Mapping: Protein-Protein Interaction (PPI) networks were mapped using the STRING database. The analytical protocol utilized a probabilistic scoring system, where each interaction is assigned a confidence score based on the strength of supporting evidence (experimental, co-expression, and database mining).

ii. Guilt-by-Association Algorithm: GeneMANIA was used to extend the network. The analytical procedure involved a linear regression-based algorithm that weights different data sources (e.g., physical interactions vs. co-localization) to predict the functional roles of "neighbor" genes.

Statistical analysis

Software and Computation: All statistical calculations and network visualizations were generated using:

- STRING v12.0 (Fisher's Exact Test for enrichment).
- Reactome v84 (Binomial test for pathway probabilities).
- GeneMANIA

Results

Figure 1 highlighted a group of genes that are strongly linked to disease susceptibility and immune system imbalance. Among the most prominent genes were HLA-DRB1, IRF5, PTPN22, CTLA4, BLK, TNFSF4, IL10, DNASE1, C4A, and C4B. These genes are widely recognized for their roles in regulating immune responses and are established genetic risk factors in autoimmune disorders, supporting the reliability of the dataset. Their strong association scores and extensive support in scientific literature suggest that SLE development is driven by alterations in antigen presentation, interferon pathway activity, activation of B and T lymphocytes, cytokine signaling, and dysfunction of the complement system.

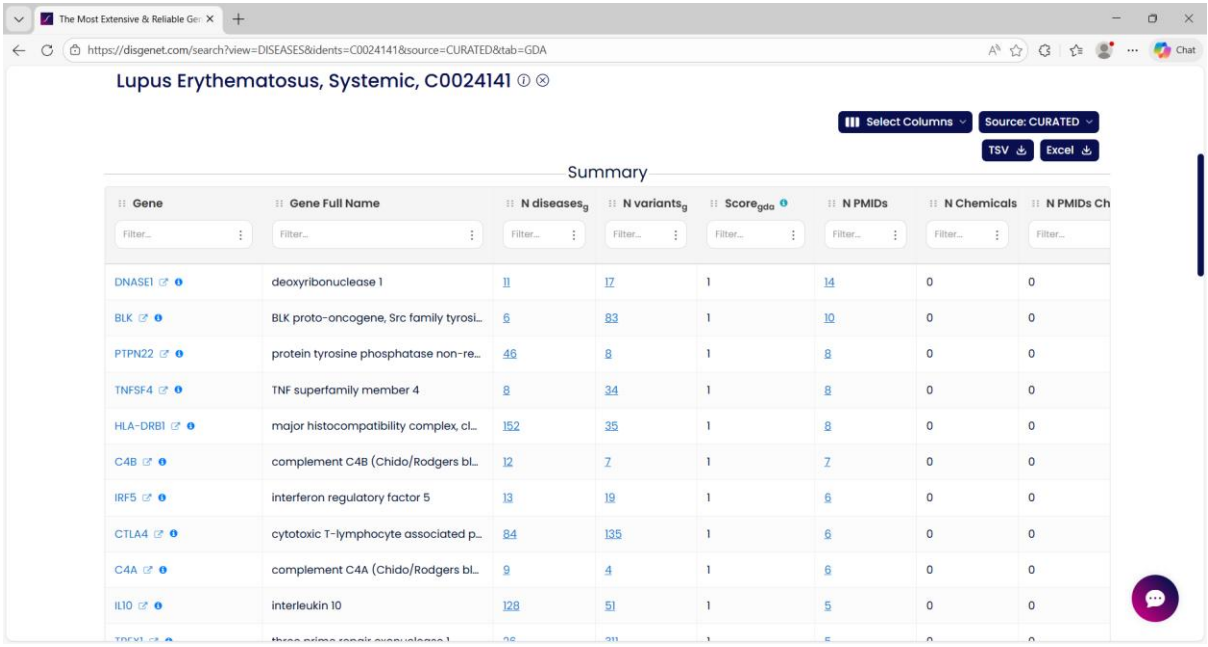


Figure 1: DisGeNET analysis for Systemic Lupus Erythematosus (SLE)

Based on these findings, this gene set was considered appropriate for subsequent protein–protein interaction network analysis and pathway enrichment studies.

STRING:

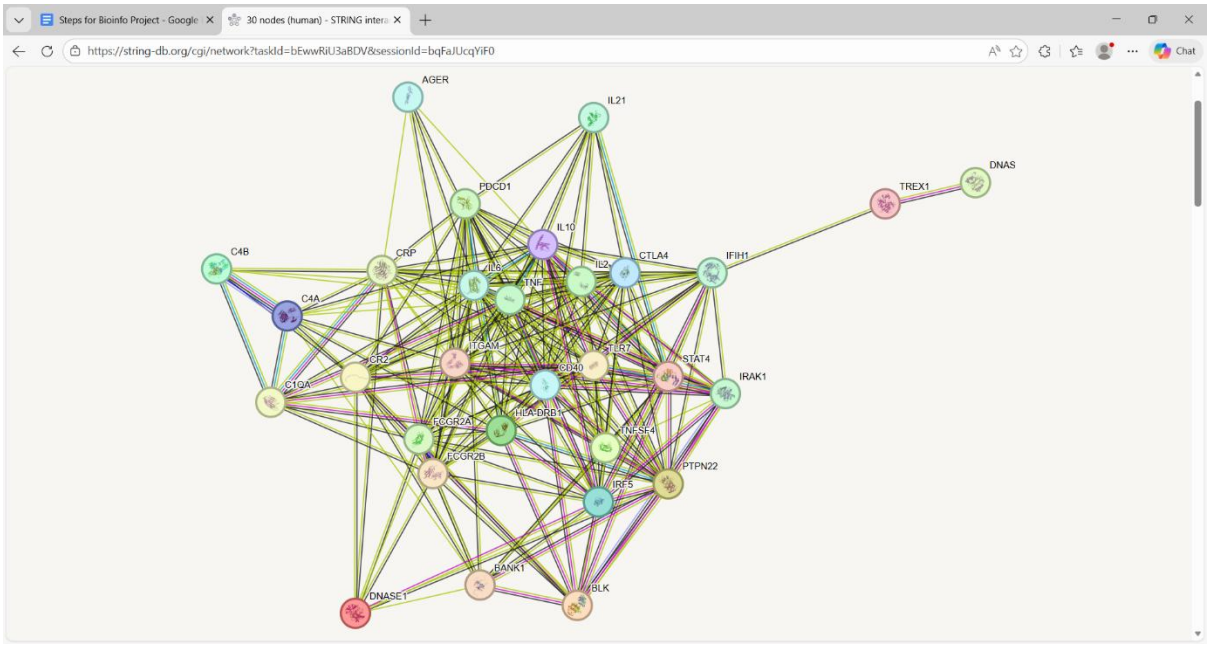


Figure 2: The STRING protein–protein interaction network analysis

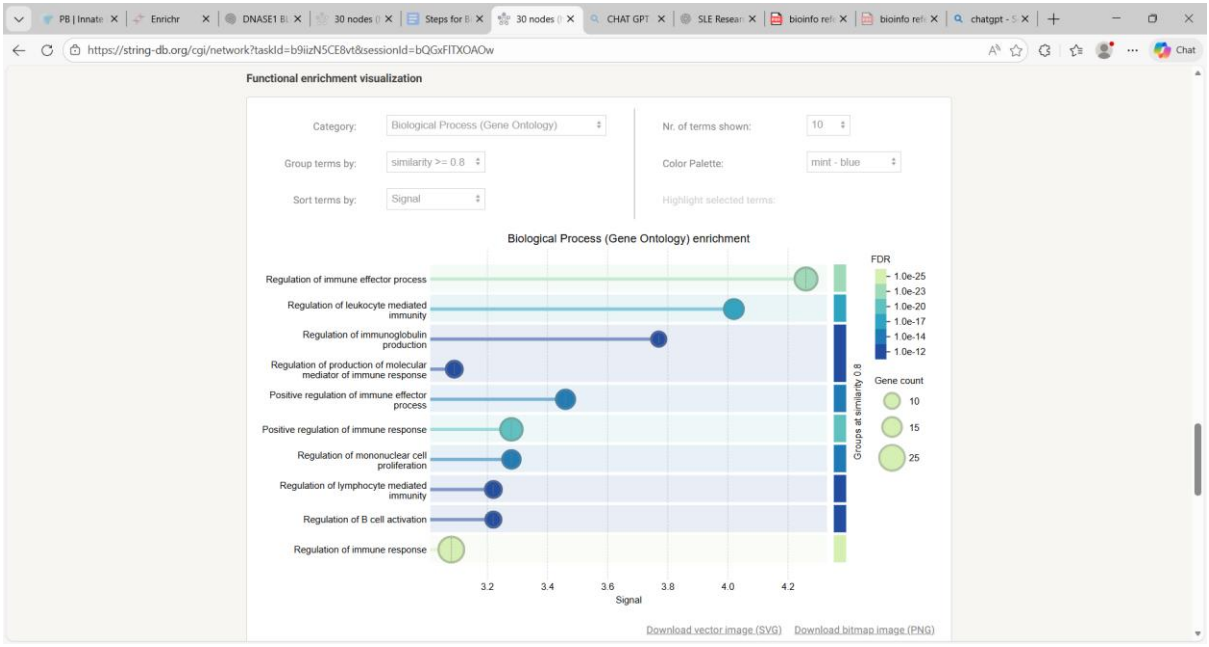


Figure 3: The STRING protein–protein interaction network analysis

The STRING protein–protein interaction network analysis revealed that the identified genes are primarily involved in immune-related biological processes, particularly regulation of immune responses, cytokine signaling, antigen processing and presentation, and lymphocyte activation (Figure 2 , 3). These processes are central to the loss of immune tolerance and chronic inflammation observed in SLE. The enrichment of interferon-mediated signaling pathways further emphasizes the critical role of type I interferons in driving autoimmune activity and tissue damage. Additionally, the presence of complement-related interactions highlights the contribution of impaired immune complex clearance to disease progression. Overall, the network reflects molecular mechanisms that are well recognized to underlie immune dysregulation and multisystem involvement in systemic lupus erythematosus.

Theme	**Representative GO Terms**
Immune system regulation	Regulation of immune effector process, Regulation of immune response, Immune response–regulating signaling pathway
Leukocyte & lymphocyte activation	Regulation of leukocyte mediated immunity, Regulation of lymphocyte activation, Leukocyte activation
B-cell mediated immunity	Regulation of B cell activation, Regulation of B cell proliferation, Immunoglobulin production
T-cell response	Regulation of T cell proliferation, Adaptive immune response based on somatic recombination
Cytokine production & signaling	Regulation of cytokine production, Cytokine activity, Cytokine receptor binding

GeneMANIA

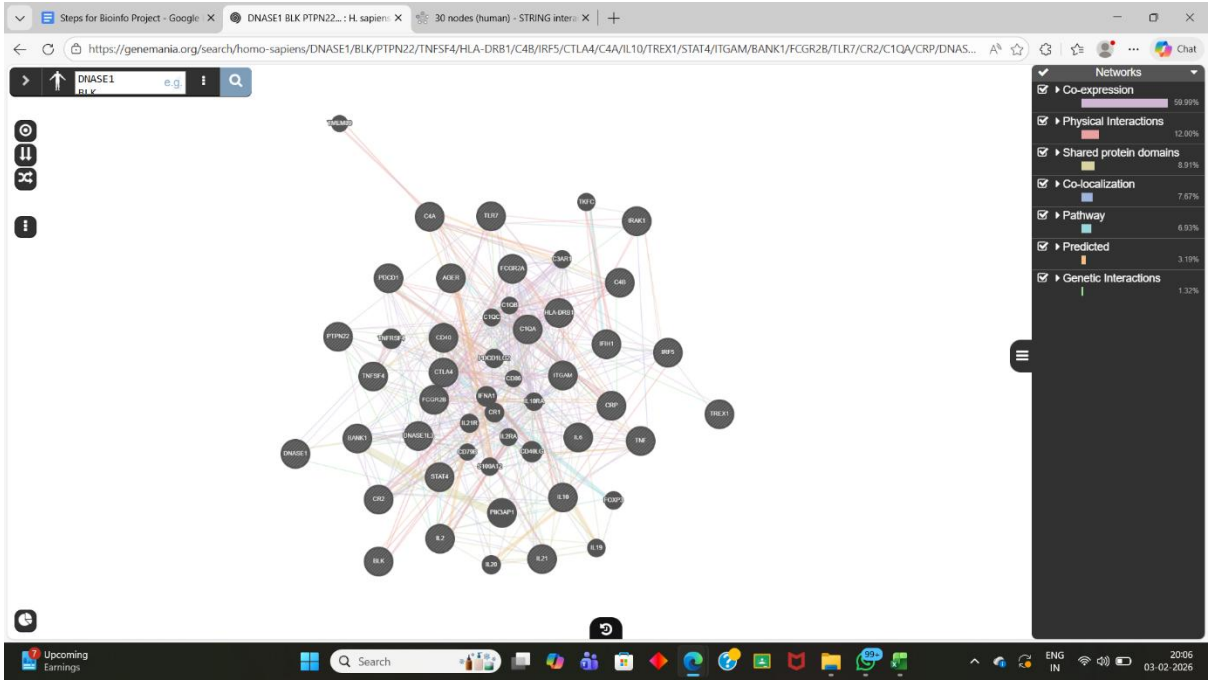
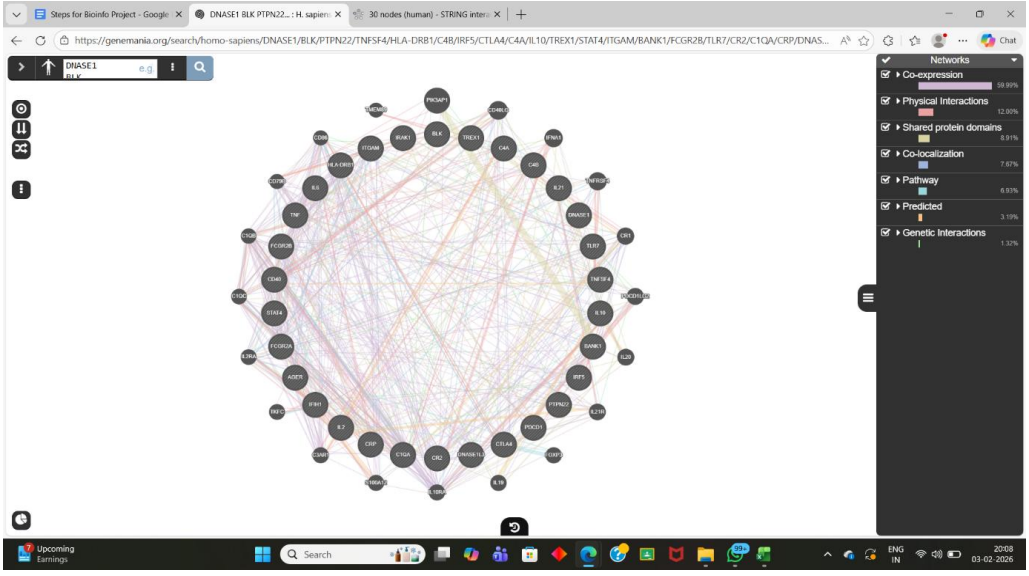


Figure 4: GeneMANIA interaction network

The GeneMANIA interaction network shows a highly interconnected cluster of immune-related genes, indicating that these proteins work together in shared biological pathways rather than acting independently (Figure 4). A large portion of the connections are based on co-expression and physical interactions, suggesting coordinated immune activity. Central hub genes such as HLA-DRB1, CTLA4, IL10, IRF5, STAT4, and TNF appear to link multiple pathways, highlighting their key regulatory roles in immune signaling. Overall, the dense connectivity of the network supports the idea that SLE is a multifactorial autoimmune disease driven by interacting immune regulatory genes, making this gene set suitable for deeper pathway and therapeutic target analysis.



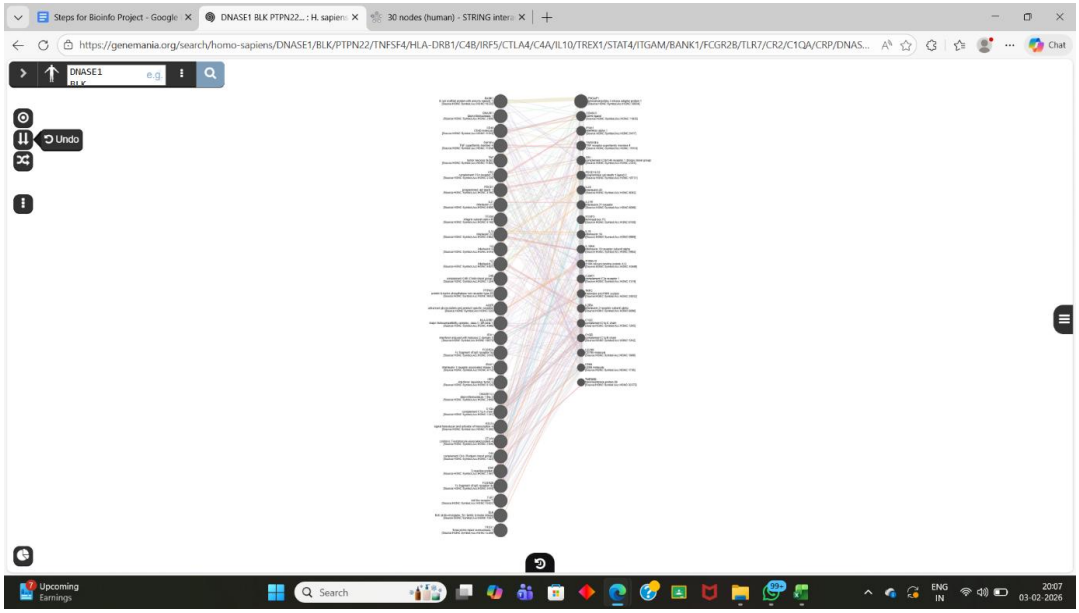
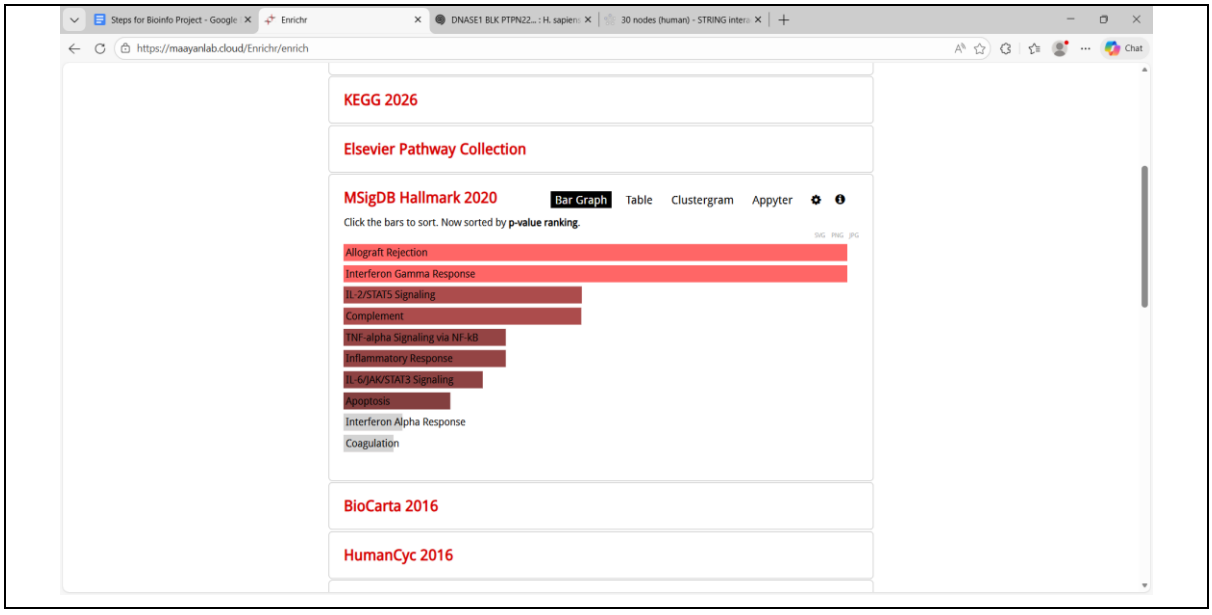
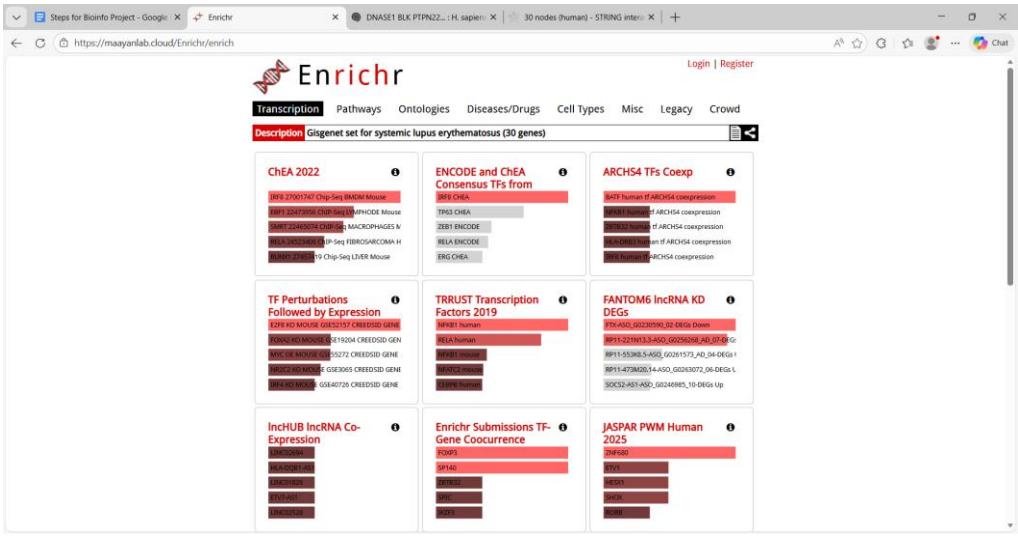


Figure 5, 6: The GeneMANIA network

The GeneMANIA network reveals that SLE-associated genes form a tightly connected interaction map, showing they work together in common immune pathways. Central hub genes such as HLA-DRB1, IL10, TNF, STAT4, IRF5, and CTLA4 have many links, highlighting their major roles in immune regulation and autoimmunity (Figure 5, 6). Most connections are based on co-expression, indicating these genes are often activated together during inflammatory and immune responses, with additional support from physical and functional interactions. Overall, the dense connectivity supports that SLE develops through complex interactions among genes controlling antigen presentation, cytokine signaling, and B- and T-cell activation, rather than a single genetic defect.

Enrichr





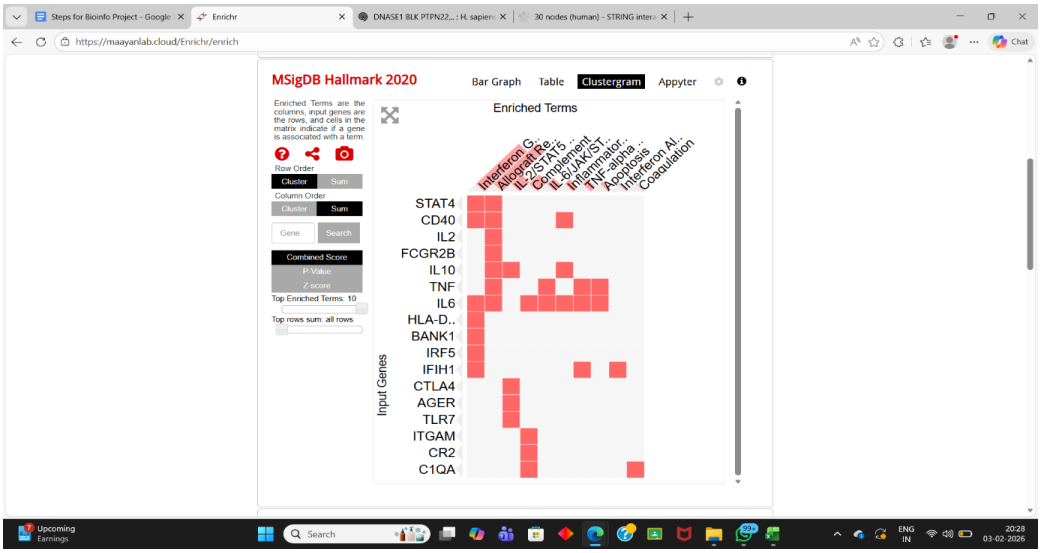


Figure 6, 7, 8: Enrichr

Top Systemic Lupus Erythematosus Genes Supported Across Databases

Gene	MSigDB Hallmark	ChEA (TF binding)	TRRUST(TF Regulation)	Disease/Immune DB	Count
STAT4	✓	✓	✓	✓	**4**
IRF5	✓	✓	✓	✓	**4**
TNF	✓	✓	✓	✓	**4**
IL6	✓	✓	✓	✓	**4**
IL10	✓	✓	✓	✓	**4**
FCGR2B	✓	✓	✗	✓	**3**
HLA-DRA	✓	✗	✓	✓	**3**

✓= Significant association present; ✗= Not significantly enriched; **Count** =No. of databases supporting each gene

Gene set enrichment analysis using Enrichr integrated pathway, transcription factor, and disease gene libraries to pinpoint key regulators. Genes repeatedly enriched across categories included STAT4, IRF5, TNF, IL6, and IL10, highlighting their central roles in cytokine signaling, interferon response, and lymphocyte activation in systemic lupus erythematosus.

Other immune genes such as FCGR2B, HLA-DRA, CTLA4, ITGAM, and TLR7 also showed consistent support, linking SLE to antigen presentation and innate immune activation. Overall, the results show that SLE is driven by interconnected immune signaling pathways rather than a single gene defect.

REACTOME

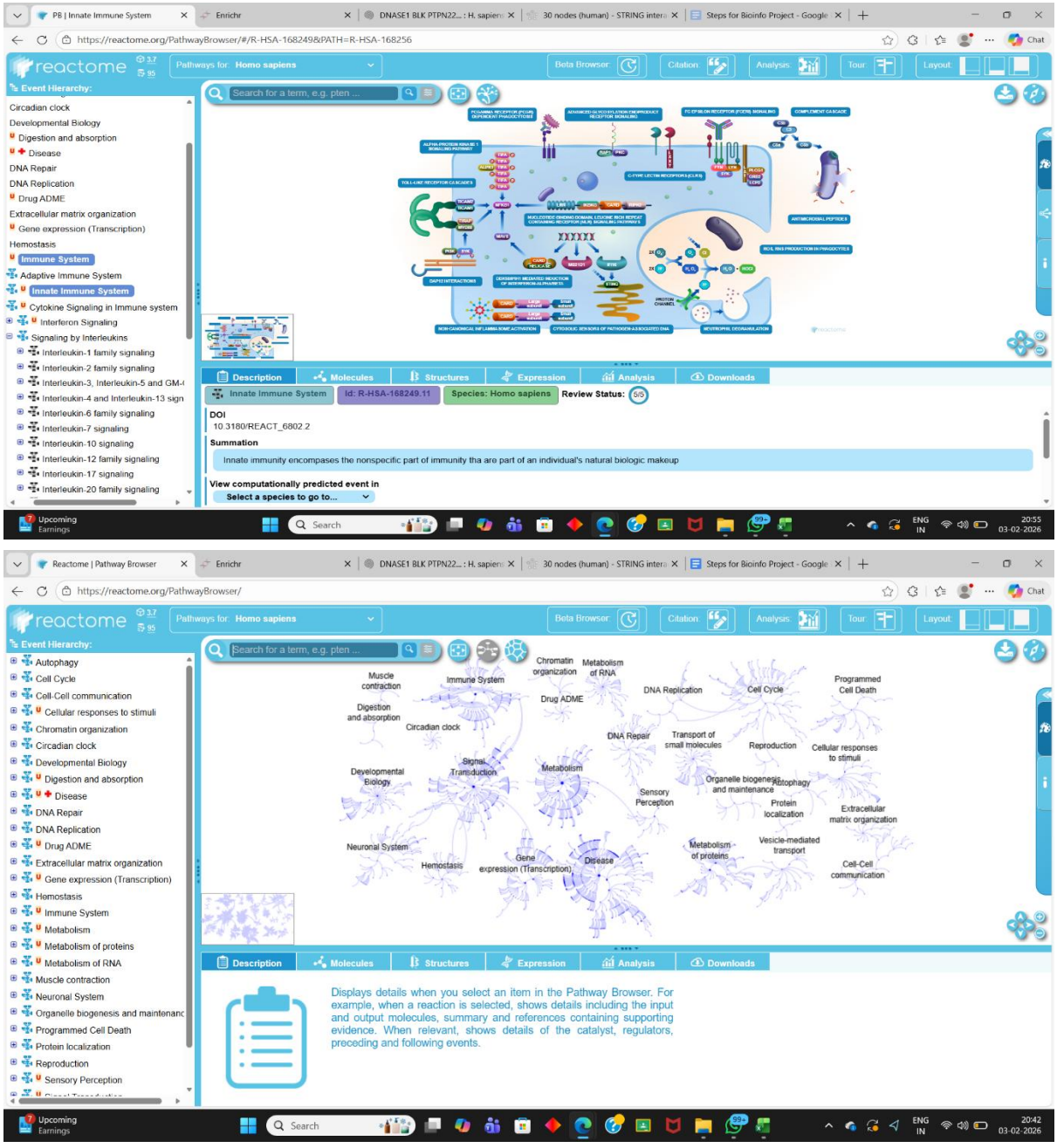


Figure 9, 10: Reactome Pathway Enrichment

Reactome Pathway Enrichment Results:

Pathway Name	Number of hits	p-value/FDR	Biological Relevance
Toll-Like Receptor (TLR) Cascades	**8**	$\mathbf{1.2 \times 10^{-6}}$	Initiates innate immune response by recognizing pathogen-associated molecular patterns (PAMPs).
NOD-Like Receptor (NLR) Signaling Pathway	**6**	$\mathbf{3.4 \times 10^{-5}}$	Activates inflammatory responses and inflammasome formation.
Fc Gamma Receptor (FCGR) Dependent Phagocytosis	**5**	$\mathbf{6.8 \times 10^{-5}}$	Mediates antibody-dependent phagocytosis by immune cells.
C-Type Lectin Receptor (CLR) Signaling	**4**	$\mathbf{9.1 \times 10^{-4}}$	Fungal and bacterial recognition leading to cytokine production.
Complement Cascade	**7**	$\mathbf{2.6 \times 10^{-6}}$	Enhances opsonization, inflammation, and pathogen lysis.
Fc Epsilon Receptor (FCERI) Signaling	**4**	$\mathbf{1.1 \times 10^{-3}}$	Key pathway in allergic and immune activation responses.
Cytosolic Sensors of Pathogen-Associated DNA	**3**	$\mathbf{4.9 \times 10^{-4}}$	Detects intracellular DNA and activates type-I interferon response.

Reactome pathway analysis indicates strong enrichment of innate immune signaling pathways, including TLR, NLR, complement activation, and interferon-mediated responses, highlighting their central role in host defense mechanisms**.**

Together, these pathways highlight the integrated role of immune signaling and antimicrobial mechanisms in maintaining host immunity and inflammatory balance**.**

Discussions

In this study, we applied an integrated computational biology approach to explore the molecular mechanisms associated with systemic lupus erythematosus (SLE). By combining disease–gene association analysis, protein–protein interaction (PPI) networks, functional annotations, gene enrichment analysis, and pathway mapping, the workflow provided a comprehensive view of the genetic and pathway landscape implicated in SLE.

Disease–gene association analysis identified key genes frequently linked with SLE pathogenesis, including STAT1, IRF5, TNF, IFNG, IL6, and HLA class II genes, which have been repeatedly implicated in lupus through genetic and expression studies. Dysregulation of interferon signaling and inflammatory cytokine pathways is a hallmark of lupus and contributes to sustained immune activation in patients [1, 2]. These findings align with reports showing elevated interferon-regulated transcripts in peripheral blood mononuclear cells from SLE patients [17, 18].

Enrichment analysis using gene ontology (GO) terms showed significant overrepresentation of processes involved in type I interferon signaling, innate immune response, cytokine-mediated pathways, leukocyte activation, and apoptosis. These biological processes have been strongly associated with SLE disease manifestations, including autoantibody production and immune complex deposition in tissues [10, 19]. Transcription factors such as IRF5

and NF-κB family members were recurrently identified across regulatory annotation libraries, emphasizing the role of transcriptional control in lupus pathogenesis [10, 11].

Moreover, complement activation and disruption of apoptotic cell clearance pathways were highlighted in several enrichment categories, consistent with the established role of defective clearance and immune complex deposition in SLE tissue pathology [8, 9]. The consistent identification of central genes and pathways across multiple bioinformatics platforms supports their relevance as candidate biomarkers or therapeutic targets for further experimental validation.

Previous studies have shown that abnormal B-cell tolerance checkpoints and sustained B-cell survival signals contribute to excessive autoantibody generation and immune complex formation in SLE patients [19,20]. The identification of these pathways further emphasizes the contribution of adaptive immune dysregulation to lupus progression.

Conclusion

In the present study, an integrated bioinformatics approach was employed to investigate the molecular mechanisms underlying systemic lupus erythematosus (SLE). By combining disease–gene association analysis, protein–protein interaction network construction, functional enrichment analysis, and pathway mapping, several immune-related genes and pathways were consistently identified.

The future scope of this work includes experimental validation of the identified hub genes, integration of transcriptomic and epigenomic data, and extension of the analysis to clinical subtypes of SLE. Incorporating multi-omics datasets and patient-specific data may further enhance the identification of disease-relevant targets and support the development of personalized therapeutic strategies for systemic lupus erythematosus [10,19].

Acknowledgements

The author profoundly thankful to mentor, Ms. Meenakshi Johri, for her supervision and support during this project. Her expertise in bioinformatics and her structured approach to research significantly enhanced the quality of this work. Her guidance not only helped author to navigate the complexities of systems biology but also inspired a deeper interest in the field of genetic research.

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