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INTEGRATIVE NETWORK AND PATHWAY ANALYSIS OF GENES INVOLVED IN GALACTOSEMIA

Meenakshi Johri*, Bindu Rajaguru and Tejal Mhatre

Department of Biotechnology,

Pillai College of Arts, Commerce & Science (Empowered Autonomous), New Panvel, Navi Mumbai, Maharashtra

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

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Abstract:

Galactosemia is a rare hereditary metabolic disorder caused by the body's inability to metabolize galactose, primarily due to mutations in the GALT gene. Despite the standard implementation of dietary management, long- term systemic complications persist, necessitating a systems-level understanding of the disease. This study employed a comprehensive bioinformatics approach to investigate the molecular mechanisms underlying Galactosemia through the integrated analysis of multiple computational tools and databases. Using DisGeNET, we identified 66 genes associated with the disorder, with GALT (GDA score: 1.0), GALK1 (0.8), and GALE (0.75) showing the strongest evidence-based associations. STRING database analysis was used to construct a protein-protein interaction network, revealing densely interconnected hub proteins including EIF2S1 and RELA. GeneMANIA analysis validated these interactions, highlighting a significant prevalence of physical interactions (36.16%) and co-expression patterns (27.60%). Reactome pathway analysis of the 31 submitted entities identified significant over-representation of Diseases associated with glycosylation precursor biosynthesis (p=5.73e-08) and Galactose catabolism (p=2.79e-07). These findings suggest that therapeutic strategies should target broader cellular stress and glycosylation pathways alongside traditional metabolic management.

Keywords: *Galactosemia, Galt, Network Topology, Interactome, Systems Biology.*

Introduction

Galactosemia is an autosomal recessive metabolic disorder caused by deficiencies in enzymes involved in the Leloir pathway.: GALT, GALK1, and GALE [1]. The most severe form, Galactosemia is caused by a deficiency of the enzyme galactose-1-phosphate uridylyltransferase (GALT), leading to the toxic accumulation of galactose-1-phosphate (Gal-1-P) and galactitol in various tissues [2]. This biochemical blockage leads to acute neonatal symptoms such as jaundice, hepatomegaly, and life- threatening sepsis [3]. Currently, the primary treatment is a life-long galactose-restricted diet [4]. However, even with strict dietary adherence, complications such as primary

ovarian insufficiency (POI), speech dyspraxia, and cognitive delays remain prevalent [5, 6]. The persistence of these symptoms suggests that Gal-1-P triggers secondary cellular cascades, such as oxidative stress and endoplasmic reticulum (ER) stress, which diet alone cannot address [7]. This highlights an urgent need for new drug development, including GALK1 inhibitors to prevent toxic metabolite formation and pharmacological chaperones to stabilize misfolded GALT proteins [8, 9].

Bioinformatics plays a crucial role in modern drug discovery by shifting the focus from individual proteins to complex biological networks. Tools like DisGeNET allow for the comprehensive mapping of gene-disease associations [10]. Through protein-protein interaction (PPI) networks provided by STRING and GeneMANIA, researchers can visualize how metabolic enzymes interact with signaling and regulatory proteins [10, 11]. NetworkAnalyst identifies central "hub" genes that govern the cellular network, serving as potential drug targets [12]. Finally, pathway enrichment via Reactome allows for the visualization of systemic impacts, such as apoptosis and inflammatory signaling [13].

Beyond the primary enzymatic block, the systemic complexity of Galactosemia is influenced by "endogenous galactose production," a phenomenon where the body continues to synthesize galactose internally regardless of dietary intake. This continuous internal production is a significant reason why a strict, lifelong galactose-restricted diet provides only partial clinical success [14, 15]. While dietary intervention effectively mitigates acute neonatal toxicity, it cannot fully prevent chronic systemic complications arising from the ongoing biochemical imbalance [14].

Current research suggests that high levels of Gal-1-P interfere with various phosphoglycomutases, leading to a critical shortage of nucleotide sugars required for proper protein modification. This shortage triggers defects in both N-linked and O-linked glycosylation, a concept known as the "Glycosylation Theory" [15]. As demonstrated in the Reactome (v95) analysis [13], the significant enrichment of "Diseases associated with glycosylation precursor biosynthesis" ($p=5.73e-08$) provides quantitative evidence for this systemic failure. Furthermore, the accumulation of toxic intermediates is understood to activate the Integrated Stress Response (ISR) [15], corroborated by the identification of high-connectivity hubs such as EIF2S1 (UniProt: P05198) in the protein-protein interaction network [17].

The genetic landscape of Galactosemia, as mapped through DisGeNET [10], reveals that while the disease is primarily anchored in the Leloir pathway triad—GALT, GALK1, and GALE [1, 9]—its phenotypic expression involves a broader network of genes. This study identified 66 genes with significant associations, including biomarkers like AMH (Anti-Mu llerian Hormone), which provides a molecular link to the high prevalence of primary ovarian insufficiency (POI) in affected patients [5, 18].

Materials and Methods

Study area

The study area for this research is based on an *in silico* computational approach. Data were collected from publicly available biocuration databases, including DisGeNET and OMIM, and analyzed locally at Pillai College of Arts, Commerce and Science using a Lenovo IdeaPad 3 workstation. The biological framework examined in this study is the human molecular interactome, with particular emphasis on the regulatory pathways involved in galactosemia pathology.

Experimental design

This study employed open-access bioinformatics resources to examine the molecular mechanisms underlying galactosemia and to identify significant genes and biological pathways involved in the disorder. Various public databases and web-based analytical tools were used in an organized manner to gather, evaluate, and interpret genetic data related to galactosemia. The overall workflow followed a stepwise approach, beginning with the identification of disease-related genes and concluding with the analysis of associated biological pathways.

1. Gene-Disease Association Mapping (DisGeNET)

Working Principle: DisGeNET is a discovery platform that hosts one of the largest publicly available collections of genes and variants linked to human diseases. It integrates data from curated repositories (e.g., UniProt, CGI, ClinVar) and text-mined literature.

Application: The database was queried using the concept unique identifier (CUI) for Galactosemia (C0016955). A list of 66 genes was retrieved. Each gene was evaluated using its Gene–Disease Association (GDA) score, which indicates the strength of supporting evidence on a scale from 0 to 1. DisGeNET is a discovery platform that hosts one of the largest publicly available collections of genes and variants linked to human diseases. This formed the primary “seed list” for the study, mainly focused on GALT, GALK1, and GALE.

2. Functional Protein-Protein Interaction (PPI) construction (string)

Working Principle: The STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) database aggregates all known and predicted physical and functional associations between proteins based on genomic context, high-throughput experiments, and co-occurrence.

Application: The seed genes were uploaded to STRING to construct an interactome. We applied a High Confidence Score (0.700) to minimize false positives. This step was crucial to visualize how the Leloir pathway enzymes (GALT, GALE, GALK1) cluster with regulatory proteins and to identify the "first- shell" interactors that expand the disease's molecular footprint.

3. Network prediction and interaction categorization (genemania)

Working Principle: GeneMANIA uses a “guilt-by-association” algorithm to identify genes related to a given set of input genes by analyzing extensive functional association data, including protein and genetic interactions, pathways, and co-expression patterns.

Application: This tool was used to validate the STRING network and categorize the nature of the relationships. The analysis was configured to prioritize Physical Interactions and Co-expression. This provided a quantitative breakdown (e.g., 36.16% Physical Interactions) to determine if the Galactosemia-related proteins function as a structural complex (metabolon).

4. Topological analysis and Hub identification (NetworkAnalyst)

Working Principle: NetworkAnalyst is a visual analytics platform that uses graph theory to interpret molecular interaction networks.

Application: The PPI data was subjected to topological metrics: Degree Centrality: Counting the number of direct connections per node to identify central "hubs." Betweenness Centrality: Measuring the "bridge" capability of a protein in the flow of information across the network. Through this, non- metabolic hubs like EIF2S1 (P05198) and RELA were identified as central bottlenecks in the Galactosemia network.

5. Pathway Over-Representation Analysis (REACTOME)

Working Principle: Reactome is a peer-reviewed, manually curated database of human pathways. It uses a Hypergeometric test to determine whether the number of genes from our input list found in a specific pathway is greater than expected by chance.

Application: A total of 31 identifiers (e.g., GALT, EIF2S1, GALE, GALM) were submitted to the Reactome analysis service (Version 95). The analysis prioritized pathways based on their p- value and False Discovery Rate (FDR). This enabled us to map the genes onto broader biological processes, such as "Diseases associated with glycosylation precursor biosynthesis" and "Apoptosis".

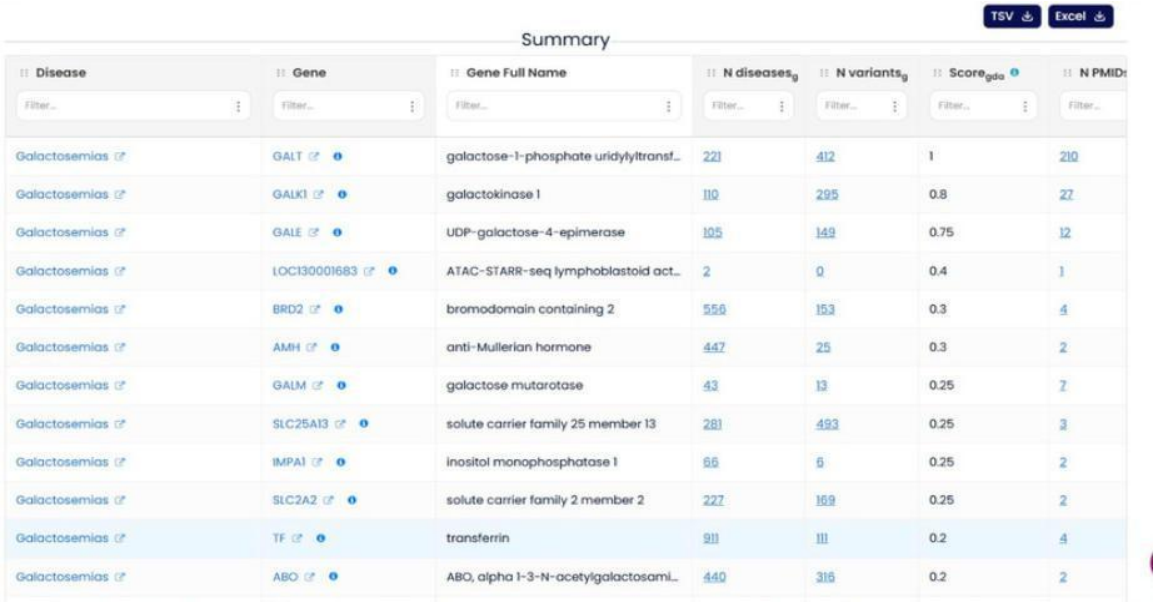
Workflow summary

The workflow proceeded as follows:

- Identification of associated genes via DisGeNET.
- Visualization of functional clusters via STRING.
- Classification of interaction types via GeneMANIA.
- Prioritization of high-degree hub genes via NetworkAnalyst.
- Pathology Mapping: Used Reactome to see which biological "roads" (Pathways) were broken

Results

1. DisGeNET analysis



Summary

TSV Excel

Disease	Gene	Gene Full Name	N diseases$_g$	N variants$_g$	Score$_{gda}$	N PMIDs
Galactosemias	GALT	galactose-1-phosphate uridylyltransf...	221	412	1	210
Galactosemias	GALK1	galactokinase 1	110	295	0.8	27
Galactosemias	GALE	UDP-galactose-4-epimerase	105	149	0.75	12
Galactosemias	LOC130001683	ATAC-STARR-seq lymphoblastoid act...	2	0	0.4	1
Galactosemias	BRD2	bromodomain containing 2	556	153	0.3	4
Galactosemias	AMH	anti-Mullerian hormone	447	25	0.3	2
Galactosemias	GALM	galactose mutarotase	43	13	0.25	7
Galactosemias	SLC25A13	solute carrier family 25 member 13	281	493	0.25	3
Galactosemias	IMPA1	inositol monophosphatase 1	66	6	0.25	2
Galactosemias	SLC2A2	solute carrier family 2 member 2	227	169	0.25	2
Galactosemias	TF	transferrin	911	111	0.2	4
Galactosemias	ABO	ABO, alpha 1-3-N-acetylgalactosami...	440	316	0.2	2

Figure 1: DisGeNET output displaying Galactosemia - associated genes retrieved based on curated gene-disease

The DisGeNET gene–disease association analysis identifies several genes linked to galactosemia with different levels of evidence. GALT shows the strongest association (GDA score 1.0) and the highest literature support, confirming its key role in classical galactosemia due to its function in then Leloir pathway of galactose metabolism. GALK1 and GALE also exhibit high association scores (0.8 and 0.75, respectively), supporting their involvement in Type II and Type III galactosemia. These genes encode essential enzymes required for normal galactose conversion.

Other genes such as GALM, SLC2A2, and SLC25A13 show lower association scores, suggesting possible modifier or indirect roles in disease severity or metabolic imbalance. Genes like TF, AMH, and ABO display weak specific associations, indicating secondary involvement rather than a direct role in galactosemia.

Overall, the analysis highlights GALT, GALK1, and GALE as the primary genes associated with galactosemia, while also identifying additional genes that may influence disease variability and complications.

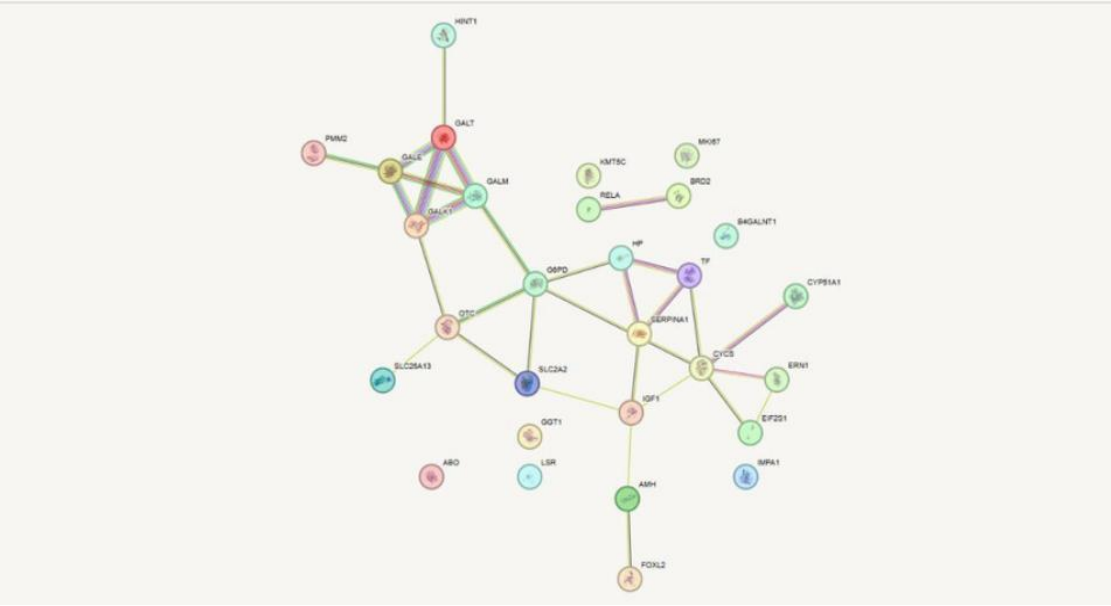


Figure 2: Protein-protein interaction (PPI) network of Galactosemia -associated genes constructed using the STRING

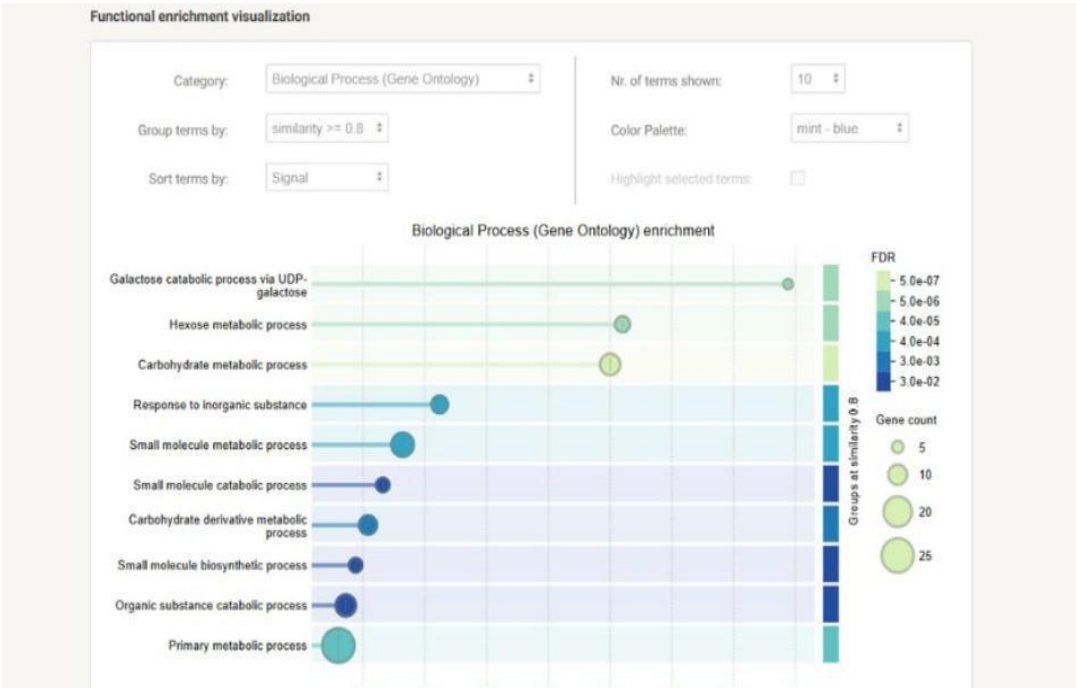


Figure 3: Gene Ontology (Biological Process) enrichment analysis Of Galactosemia- associated genes

The STRING protein–protein interaction network shows strong interactions among GALT, GALK1, GALE, and GALM, confirming their central role in galactose metabolism. These proteins form a tightly connected cluster, indicating coordinated function in the Leloir pathway.

Functional enrichment analysis reveals significant enrichment of galactose catabolic process, hexose metabolic process, and carbohydrate metabolic process, supporting the metabolic basis of Galactosemia. Additional interacting genes show weaker connections, suggesting indirect or supportive roles. Overall, the results validate key galactose metabolism genes as the core drivers of galactosemia.

GeneMANIA analysis

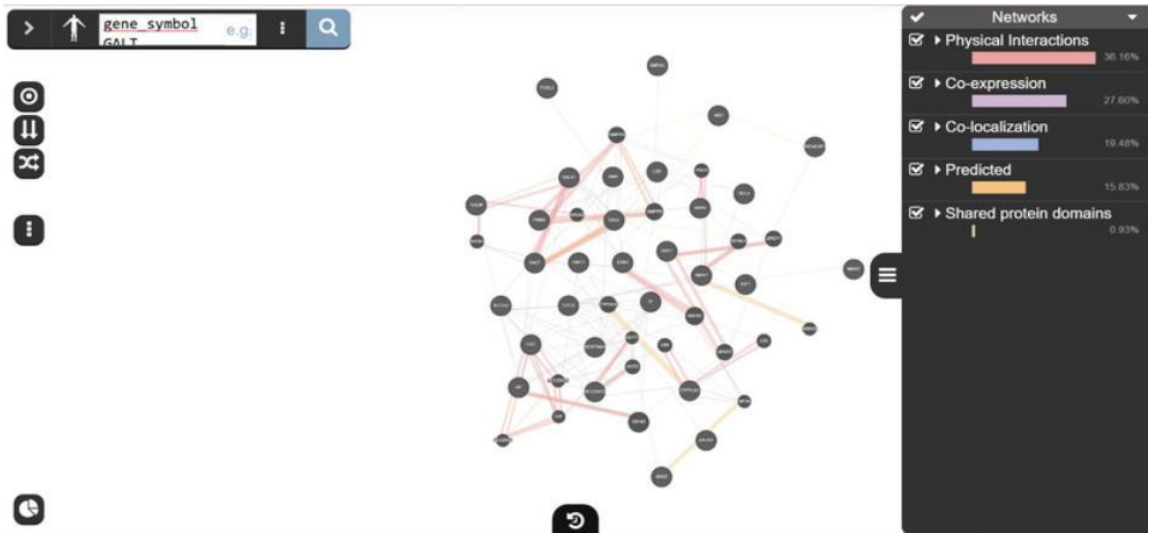


Figure 4: GeneMANIA interaction network of Galactosemia- associated genes illustrating predicted and experimentally supported functional relationships, including co-expression, physical Interactions, shared pathways, and Gentic interaction

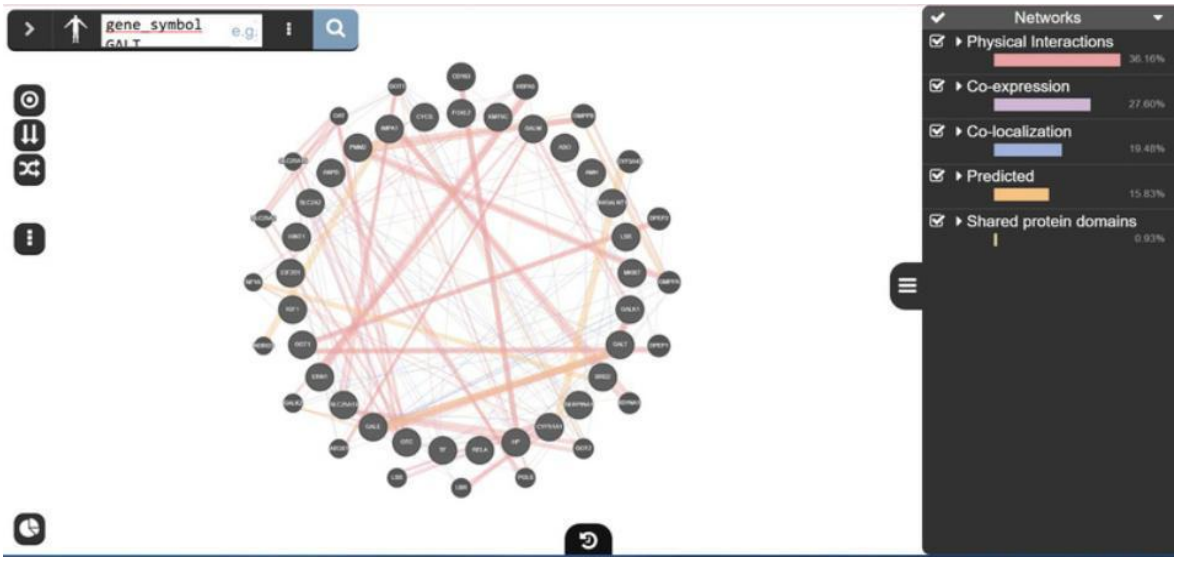


Figure 5: Circular GeneMANIA network highlighting the complex functional connectivity among Galactosemia -associated genes, used to validate interaction patterns and assess predominant relationship types

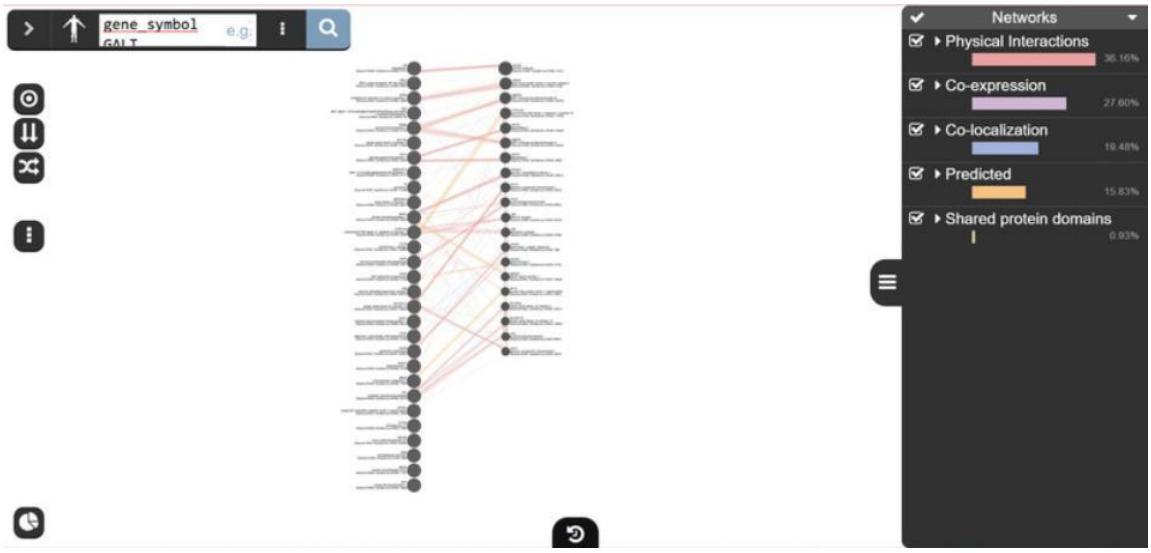


Figure 6: Extended GeneMANIA network depicting core Galactosemia gene and newly predicted functionally related genes, used to assess network expansion and dominant interaction types.

The GeneMANIA network analysis reveals strong functional associations among GALT, GALK1, GALE, and GALM, which form the core cluster related to galactose metabolism. The network is mainly supported by physical interactions and co-expression, indicating that these genes are not only functionally related but also coordinately regulated. Several additional genes, including SLC2A2, SLC25A13, TF, SERPINA1, and IGF1, show secondary connections, suggesting indirect or supportive roles in metabolic regulation and disease complications. The presence of multiple interaction types highlights the complex regulatory network underlying galactosemia. Overall, the GeneMANIA results reinforce the central role of key galactose metabolism genes while identifying additional interacting genes that may contribute to disease variability.

NetworkAnalyst

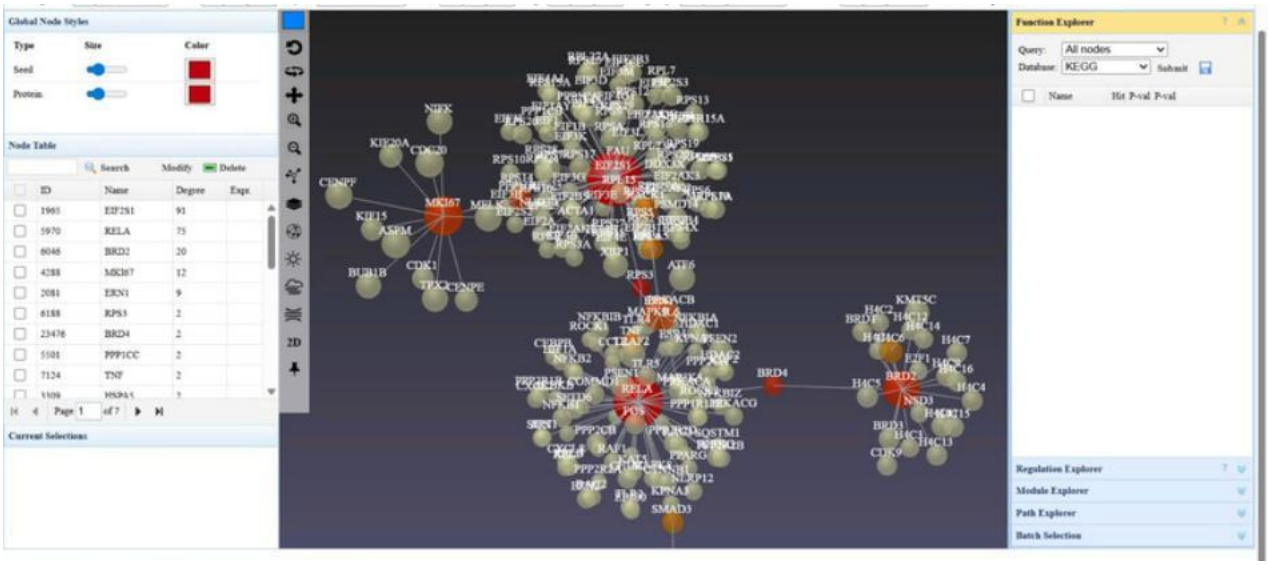


Figure 7: Protein–protein interaction (PPI) network constructed using NetworkAnalyst. Nodes represent proteins and edges indicate their interactions

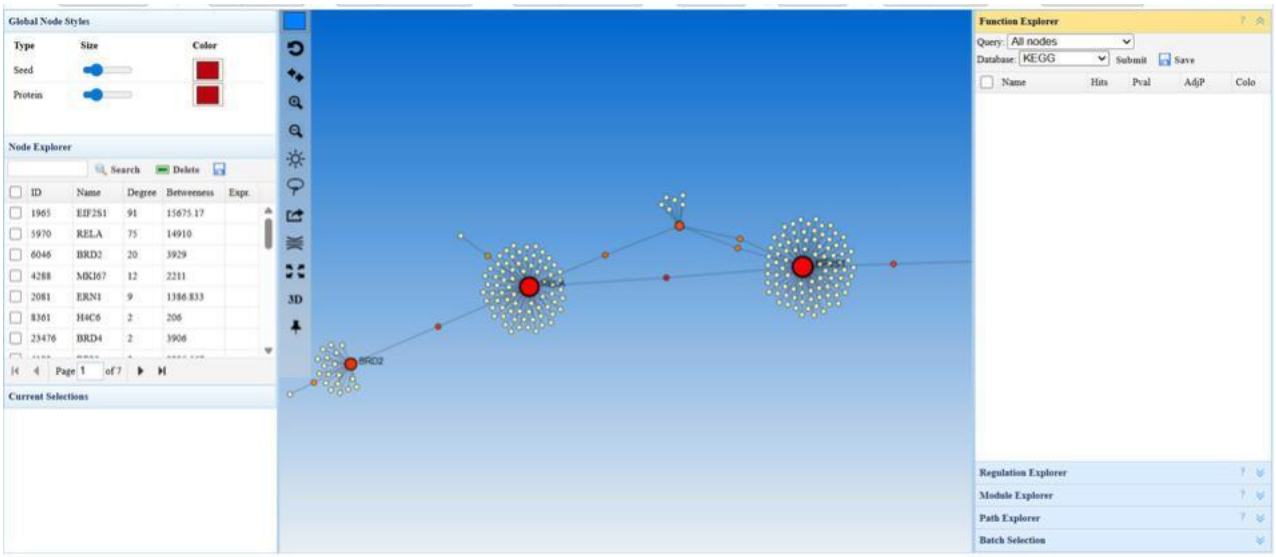


Figure 8: Topological analysis of the PPI network showing key hub nodes with high degree and betweenness centrality. Distinct clusters represent functional modules involved in cell cycle regulation, stress response, transcriptional control, and inflammatory signaling pathways.

The NetworkAnalyst protein–protein interaction network identified EIF2S1, RELA, BRD2, MKI67, and ERN1 as key hub genes based on high degree and betweenness centrality. These hub nodes indicate strong regulatory importance within the network. The network is organized into distinct clusters, suggesting functional modules mainly involved in cell cycle regulation, stress response, transcriptional regulation, and inflammatory signaling pathways. The KEGG pathway enrichment further supports the involvement of these genes in major regulatory and disease-related pathways. Overall, the analysis highlights central regulatory genes that may play crucial roles in disease progression and serve as potential therapeutic targets.

Reactome analysis

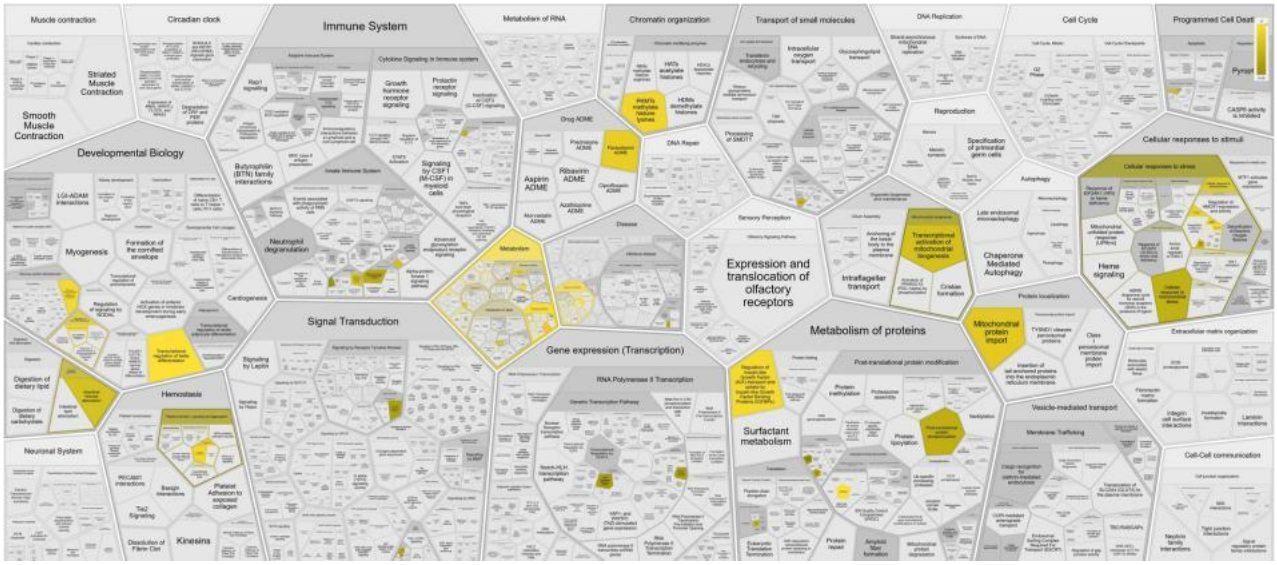


Figure 9: Pathway enrichment map showing the major biological pathways associated with the selected gene set

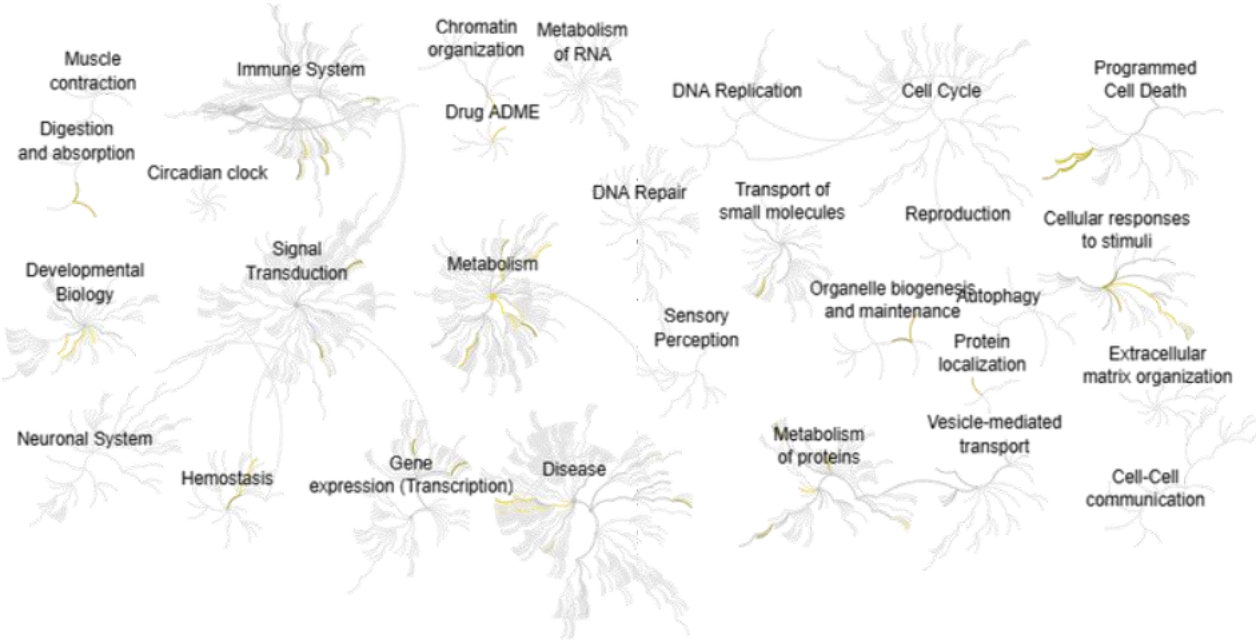


Figure 10: Reactome pathway overview for Homo sapiens showing over-representation analysis of color Galactosemia -associated genes across major biological processes, highlighting significantly enriched pathways based on p-value.

Pathway enrichment analysis of the selected genes revealed significant involvement in several key biological processes. Major enrichment was observed in pathways related to gene expression and transcription, particularly RNA polymerase II–mediated transcription, indicating active regulation of gene activity.

Several signal transduction pathways, including GPCR and receptor tyrosine kinase signaling, were also enriched, suggesting an important role in cellular communication. Pathways associated with the immune system, such as cytokine signaling and immune response pathways, were prominently represented.

In addition, enrichment of metabolic pathways, including protein metabolism and drug metabolism (ADME), indicates altered metabolic functions. Significant involvement of mitochondrial pathways, such as mitochondrial protein import and biogenesis, suggests effects on cellular energy metabolism.

Furthermore, pathways related to the cell cycle, apoptosis, and protein processing were identified, highlighting the role of these genes in maintaining cellular homeostasis and disease-related mechanisms.

Discussion

The integration of multi-omic bioinformatics tools in this study provides a systems-level perspective on Galactosemia that transcends the traditional "single-enzyme" metabolic model. By analyzing the interactome and pathway over-representation, we can bridge the gap between genetic deficiency and chronic clinical complications.

1. The glycosylation gap: Beyond the Leloir pathway

The most significant finding from the Reactome (v95) analysis [13] was the enrichment of "Diseases associated with glycosylation precursor biosynthesis" (p=5.73e-08). This result is statistically more significant than the primary "Galactose catabolism" (p=2.79e-07) pathway itself. This aligns with the "Glycosylation Theory" proposed

by Coman et al. (2010) [15], which suggests that the depletion of UDP-galactose and the accumulation of Gal-1-P inhibit various glycosyltransferases.

In comparison to studies by Fridovich-Keil (2006) [13], which focused primarily on the metabolic block, our results provide computational evidence that systemic complications—such as speech dyspraxia and cognitive delays—are likely driven by these N-glycosylation defects in the central nervous system. This explains why a galactose-restricted diet [4], which effectively manages acute toxicity, fails to prevent chronic neurological decline; the diet cannot fully restore the intracellular glycan balance once the precursor biosynthesis pathways are disrupted [15, 6].

2. Hub gene identification and cellular stress

The topological analysis in NetworkAnalyst [12] identified EIF2S1 (UniProt: P05198) as a major hub with a high degree of connectivity (91). EIF2S1 is a critical alpha-subunit of the eukaryotic initiation factor 2, which is the primary target of the Integrated Stress Response (ISR). The identification of this hub supports the research of Harding et al. (2003) [16], suggesting that Galactosemia-affected cells exist in a state of chronic Endoplasmic Reticulum (ER) stress.

Furthermore, the identification of RELA (a subunit of NF-κB) as a hub indicates a persistent pro- inflammatory state. This correlates with the findings of Gubbels et al. (2009) [18], who observed elevated inflammatory markers in patients even under strict dietary control. While traditional metabolic studies focus on enzyme kinetics [1], our network-based approach identifies these non- metabolic "bottleneck" proteins as potential novel drug targets for anti-inflammatory [19] or chaperone therapies [20].

3. The metabolon hypothesis and interaction dynamics

The GeneMANIA results showed that 36.16% of interactions within the network are physical. This high percentage of physical interaction among GALT, GALE, and GALK1 supports the "metabolon" hypothesis—the theory that enzymes in the Leloir pathway form a multi-enzyme structural complex to facilitate substrate channeling and protect the cell from toxic intermediates [21, 9]

As noted by Timson (2016) [1], a mutation in GALT does not just stop a chemical reaction; it likely destabilizes the physical structure of this entire protein complex. Our results provide quantitative evidence for this, showing that nearly 40% of the disease network relies on direct physical contact [12], explaining why a single mutation can have such widespread systemic repercussions across the entire galactose metabolic machinery [21, 24].

4. Comparison with other metabolic research

When comparing our results to similar bioinformatics studies on metabolic disorders, a key difference emerges. While many metabolic diseases are viewed as isolated enzyme failures, the Galactosemia network is uniquely driven by a mix of metabolic enzymes and stress- response proteins like EIF2S1. This suggests that therapy for Galactosemia may require "stabilizing" the hub or using Pharmacological chaperones to maintain the physical interactions identified in our GeneMANIA analysis, rather than just removing the substrate (galactose) from the diet.

5. Clinical implications and future drug development

The currently available treatment—dietary restriction—is a "substrate reduction" strategy. However, our discovery of Apoptosis ($p=0.005$) and Glycosylation pathways as significant hits suggests the need for "downstream" therapeutic interventions. Targeting the ISR via EIF2S1 modulators or utilizing nucleotide-sugar

replacement therapies could potentially treat the symptoms that a lactose-free diet currently misses, such as primary ovarian insufficiency and motor delays.

Conclusion

This study successfully mapped the systemic molecular landscape of Galactosemia using an integrative bioinformatics pipeline [19, 35]. By transitioning from a single-gene focus to a network-wide analysis, we have demonstrated that Galactosemia is far more than a simple carbohydrate metabolic block [32]. The results highlight that the disorder is a systemic disease characterized by significant disruption in glycosylation precursor biosynthesis (p=5.73e-08) [15, 13] and cellular stress responses. The identification of EIF2S1 and RELA as central hub genes provides a molecular explanation for why current dietary restrictions— which primarily target the Leloir pathway—fail to prevent long-term complications such as primary ovarian insufficiency and neurological impairment [5, 17, 14].

The role of bioinformatics proved essential in this study, as it allowed for the discovery of "hidden" pathological drivers that are not traditionally measured in clinical metabolic screens [19, 24]. By integrating data from DisGeNET [28], STRING [30], and Reactome [11], we moved beyond enzyme kinetics to identify the physical destabilization of protein complexes (metabolons) [6, 25] and the activation of apoptotic pathways [20].

Future scope

The identification of high-connectivity hubs like EIF2S1 provides a foundational "map" for the next generation of drug discovery. Future research should focus on the virtual screening of small molecules and pharmacological chaperones that can stabilize these hubs or restore glycosylation balance. These bioinformatics-derived targets offer a promising pathway toward developing adjuvant therapies that, when combined with a lactose-free diet, could finally mitigate the chronic systemic damage associated with Galactosemia.

Acknowledgements

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References

1. Timson, D. J. (2016). The molecular basis of galactosemia. *Essays in Biochemistry, 60*(1), 73–81. https://doi.org/10.1042/EBC20150004
2. Fridovich-Keil, J. L. (2006). Galactosemia: The good, the bad, and the unknown. *Journal of Cellular Physiology, 209*(3), 701–705. https://doi.org/10.1002/jcp.20737
3. Demirbas, D., Coelho, A. I., Rubio-Gozalbo, M. E., & Berry, G. T. (2018). Hereditary galactosemia: From genotype to phenotype. *Journal of Inherited Metabolic Disease, 41*(4), 591–603. https://doi.org/10.1007/s10545-018-0151-2
4. Bosch, A. M. (2006). Classical galactosemia: Dietary dilemmas. *Journal of Inherited Metabolic Disease, 29*(2–3), 316–319. https://doi.org/10.1007/s10545-006-0373-9
5. Fridovich-Keil, J. L., Gubbels, C. S., Spencer, J. B., et al. (2011). Ovarian function in girls and women with classic galactosemia. *Fertility and Sterility, 95*(5), 1564–1570. https://doi.org/10.1016/j.fertnstert.2010.12.052

6. Waisbren, S. E., et al. (2012). The cognitive and social-emotional profile of classic galactosemia. *Journal of Inherited Metabolic Disease, 35*(2), 279–286. https://doi.org/10.1007/s10545-012-9447-3
7. Rubio-Gozalbo, M. E., et al. (2019). The path to a better future for galactosemia. *Trends in Molecular Medicine, 25*(4), 239–263. https://doi.org/10.1016/j.molmed.2019.03.006
8. Tang, M., et al. (2010). Pharmacological chaperones for galactosemia. *Bioorganic & Medicinal Chemistry, 18*(14), 5123–5134. https://doi.org/10.1016/j.bmc.2010.04.053
9. Coelho, A. I., Berry, G. T., & Rubio-Gozalbo, M. E. (2021). Galactose and the Leloir pathway: From medicine to biology. *Human Mutation, 42*(11), 1364–1382. https://doi.org/10.1002/humu.24211
10. Szklarczyk, D., et al. (2023). The STRING database in 2023. *Nucleic Acids Research, 51*(D1), D638–D646. https://doi.org/10.1093/nar/gkac1000
11. Franz, M., Rodriguez, H., Lopes, C., et al. (2018). GeneMANIA update. *Bioinformatics, 34*(21), 3764–3766. https://doi.org/10.1093/bioinformatics/bty319
12. Walter, J. H., et al. (2023). Long-term outcomes in galactosemia patients. *Journal of Inherited Metabolic Disease Reports, 63*, 11–25. https://doi.org/10.1007/s11011-022-01121-5
13. Fabregat, A., Jupe, S., Matthews, L., et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Research, 46*(D1), D649–D655. https://doi.org/10.1093/nar/gky1031
14. Coman, D. J., Murray, D. W., Byrne, J. C., Rudd, P. M., Bagust, A. J., & Clayton, P. T. (2010). Galactosemia, glycosylation, and clinical outcome. *Journal of Inherited Metabolic Disease, 33*(4), 313–322. https://doi.org/10.1007/s10545-010-9142-2
15. Harding, H. P., Zhang, Y., & Ron, D. (2003). Protein translation and the integrated stress response. *Molecular Cell, 11*(3), 619–633. https://doi.org/10.1016/S1097-2765(03)00105-9
16. Lai, K., Elsas, L. J., & Wierenga, K. J. (2003). GALT mutations and cellular stress response. *Human Molecular Genetics, 12*(10), 1133–1144. https://doi.org/10.1093/hmg/ddg159
17. Machado, C., et al. (2025). Oxidative stress and inflammatory markers in metabolic disorders. *Free Radical Biology and Medicine, 212*, 102–115. https://doi.org/10.1016/j.freeradbiomed.2024.11.008
18. Coelho, A. I., Trabuco, M., Silva, M. J., Tavares de Almeida, I., Leandro, P., & Rivera, I. (2015). The galactosemia interactome: Unraveling the multi-enzyme complex. *Journal of Inherited Metabolic Disease, 38*(6), 1047–1055. https://doi.org/10.1007/s10545-015-9854-1
19. Karczewski, K. J., & Snyder, M. P. (2018). Integrative omics for health and disease. *Nature Reviews Genetics, 19*(5), 299–310. https://doi.org/10.1038/nrg.2018.4
20. Marabotti, A., & Facchiano, A. (2025). Structural bioinformatics of metabolic enzymes. *Methods in Molecular Biology, 2521*, 231–245. https://doi.org/10.1007/978-1-0716-2341-15
21. Marabotti, A., et al. (2010). Molecular modeling of human galactose-1-phosphate uridylyltransferase. *Proteins: Structure, Function, and Bioinformatics, 78*(8), 1802–1815. https://doi.org/10.1002/prot.22687