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

OPEN ACCESS

MAPPING GENE INTERACTION NETWORKS TO IDENTIFY THERAPEUTIC TARGETS IN NON-ALCOHOLIC STEATOHEPATITIS (NASH)

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Received: 20 December 2025	Revised: 22 January 2026	Accepted: 22 February 2026	Published: 28 February 2026

DOI: **https://doi.org/10.5281/zenodo.18899169**

Abstract:

Non-Alcoholic Steatohepatitis (NASH) is a progressive stage of chronic liver disease that involves inflammation and fibrosis. This study used an integrated bioinformatics approach to map gene interaction networks and find potential therapeutic targets. Disease-related genes were obtained from DisGeNET, and a Protein–Protein Interaction (PPI) network was built using STRING and GeneMANIA to include functional and co expression data. Network topology analysis through NetworkAnalyst helped identify key hub genes based on degree and betweenness centrality. Functional enrichment analysis using Reactome showed significant involvement of cytokine signaling, TGF-β–mediated fibrosis, and PPAR signaling pathways. Classification of hub genes via Pharos highlighted druggable families such as Nuclear Receptors (PPARG) and Enzymes (PTGS2). Drug–gene interaction analysis using DGIdb identified approved inhibitors like Canakinumab (IL1B), Golimumab (TNF), and Siltuximab (IL6) as potential candidates for drug repurposing. Overall, the study highlights a core inflammatory metabolic axis in NASH and suggests that targeting cytokine hubs could provide a more effective treatment strategy than general metabolic interventions (1, 2).

Keywords: *Non-Alcoholic Steatohepatitis (NASH); Protein–Protein Interaction (PPI) Network; Hub Genes; Cytokine Signaling; TGF-β Signaling Pathway.*

Introduction

The growing prevalence of metabolic dysfunction-associated liver disease has intensified the need to understand the molecular changes that lead to Non-Alcoholic Steatohepatitis (NASH). NASH differs from simple fatty liver by the presence of lobular inflammation, ballooning of liver cells, and varying levels of fibrosis. This progression is commonly explained by the "multiple-hit" hypothesis, where an initial hit of hepatic lipid accumulation is followed by secondary events involving oxidative stress, gut-derived endotoxins, and the release of pro-inflammatory cytokines (1). Identifying "hubs"—genes that have the highest level of connectivity within this biological network—is crucial for understanding how these hits are coordinated at the cellular level.

To explore this complex process, this study combines several high-throughput computational tools. DisGeNET provides the foundational evidence linking genetic variants to clinical conditions. STRING and GeneMANIA introduce a functional perspective, showing how these gene products interact or are co-expressed under stress. By applying topological filters in NetworkAnalyst, the study moves beyond simple lists of genes to find "bottleneck" genes that regulate the shift from metabolic dysfunction to fibrotic signaling. The Pharos platform further refines these targets by categorizing them into established druggable protein groups, including kinases, transcription factors, and nuclear receptors (2). Additionally, DGIdb is used to assess drug–gene interactions, helping identify actionable targets and supporting informed strategies for drug repurposing.

Finally, Reactome is used to place these hub genes within defined biochemical pathways. By cross-referencing findings across major pathway databases, such as KEGG and MSigDB, the study aims to produce a statistically strong and biologically meaningful set of therapeutic targets. Together, this systems-based approach offers a structured method for targeted interventions in NASH, a condition that still lacks fully effective pharmacological treatments.

Methodology

Seed gene identification

NASH-related genes were collected from DisGeNET using the term "Non-Alcoholic Steatohepatitis (NASH)" and were ranked based on disease association scores and evidence index. Thirty high-confidence genes, including TNF, IL6, IL1B, TGFB1, PPARG, and PNPLA3, were chosen as seed genes for further study due to their well-known roles in inflammation, metabolism, and fibrosis in NASH (3).

Table 1: Priority seed genes identified with high-confidence scores from the DisGeNET database.

Gene	Description	Score	e^i
PNPLA3	patatin like phospholipase domain containing 3	1.0	0.9464285714285714
GPT	glutamic--pyruvic transaminase	0.9	0.908256880733945
MTTP	microsomal triglyceride transfer protein	0.85	1.0
IL1B	interleukin 1 beta	0.85	0.9375
ADIPOQ	adiponectin, C1Q and collagen domain containing	0.85	0.9615384615384616
LEP	leptin	0.8	0.9111111111111111
NR1H4	nuclear receptor subfamily 1 group H member 4	0.8	0.9871794871794872
NLRP3	NLR family pyrin domain containing 3	0.8	0.9444444444444444
CYP2E1	cytochrome P450 family 2 subfamily E member 1	0.8	0.9545454545454546

TM6SF2	transmembrane 6 superfamily member 2	0.8	0.9583333333333334
TNF	tumor necrosis factor	0.8	0.896551724137931
IL6	interleukin 6	0.8	0.7647058823529411
SAMM50	SAMM50 sorting and assembly machinery component	0.8	1.0
FGF21	fibroblast growth factor 21	0.75	0.9111111111111111
TGFB1	transforming growth factor beta 1	0.75	0.9523809523809523
SREBF1	sterol regulatory element binding transcription factor 1	0.75	1.0
ALDH2	aldehyde dehydrogenase 2 family member	0.75	1.0
PPARA	peroxisome proliferator activated receptor alpha	0.75	0.9791666666666666
SIRT1	sirtuin 1	0.75	1.0
NFE2L2	NFE2 like bZIP transcription factor 2	0.75	0.9583333333333334
PPARG	peroxisome proliferator activated receptor gamma	0.75	0.96875
PTEN	phosphatase and tensin homolog	0.75	0.9375
SERPINA1	serpin family A member 1	0.75	0.8181818181818182
HFE	homeostatic iron regulator	0.75	0.6470588235294118
LEPR	leptin receptor	0.75	0.8
AHR	aryl hydrocarbon receptor	0.7	1.0
INS	insulin	0.7	1.0
JAK2	Janus kinase 2	0.7	1.0
SOD2	superoxide dismutase 2	0.7	1.0
DGAT2	diacylglycerol O-acyltransferase 2	0.7	1.0

Protein–Protein Interaction (PPI) network analysis

Protein–protein interaction networks for the selected seed genes were created using the STRING database.

STRING combines known and predicted interactions from curated databases, experimental data, and computational predictions. To reduce the number of false-positive interactions and focus on biologically relevant relationships connected to non-alcoholic steatohepatitis (NASH), only high-confidence interaction scores were included (4).

Functional network expansion using GeneMANIA

The initial PPI network was expanded using GeneMANIA by adding genes that have functional associations with the seed genes, such as co-expression, physical interactions, genetic interactions, and shared pathway involvement.

This method helped identify co-factors and secondary regulatory genes that may contribute to the progression of non-alcoholic steatohepatitis (NASH), even though they are not prominently featured in standard disease association databases (2).

Topological analysis and hub gene identification using NetworkAnalyst

The topology of the expanded interaction network was examined using NetworkAnalyst. Key metrics like degree centrality and interaction centrality were calculated to pinpoint hub genes (5). Genes with high centrality values

were seen as influential regulatory points due to their significant role in maintaining network stability and facilitating the transfer of information.

Pathway mapping using Reactome

Reactome was used to perform pathway enrichment analysis to identify biological pathways that were significantly enriched among the hub genes. Pathways with a false discovery rate (FDR)-adjusted p-value lower than 0.05 were considered statistically significant. This analysis gave insight into the molecular mechanisms disrupted in non-alcoholic steatohepatitis (NASH) and supported the biological interpretation of the network-based findings.

Network-based hub gene identification and functional prioritization

Hub genes were identified through a network-based strategy based on the idea that genes located at central positions in molecular networks have important regulatory functions. Topological factors were used to assess the connectivity and influence of genes within the network. Enrichr was also used to strengthen hub selection by examining consistent functional enrichment patterns. Finally, genes showing strong topological significance and repeated appearance across various enrichment and pathway databases were chosen as the main hub genes(6).

Results

DisGeNET – Seed gene selection

Summary

Gene	Gene Full Name	N diseases$_g$	N variants$_g$	Score$_{gda}$	N PMIDs
PNPLA3	patatin like phospholipase domain c...	17	61	1	3
GPT	glutamic--pyruvic transaminase	7	3	0.9	1
MTTP	microsomal triglyceride transfer prot...	12	221	0.85	1
IL1B	interleukin 1 beta	166	5	0.85	1
ADIPOQ	adiponectin, C1Q and collagen doma...	44	6	0.85	1
LEP	leptin	63	70	0.8	2
NR1H4	nuclear receptor subfamily 1 group H ...	21	14	0.8	2
NLRP3	NLR family pyrin domain containing 3	40	454	0.8	1
CYP2E1	cytochrome P450 family 2 subfamily ...	48	9	0.8	1
TM6SF2	transmembrane 6 superfamily mem...	4	4	0.8	1
TNF	tumor necrosis factor	312	9	0.8	1
IL6	interleukin 6	214	9	0.8	0
SAMM50	SAMM50 sorting and assembly mach...	2	6	0.8	0

Figure 1: Seed genes with higher confidence extracted from DisGeNET web tool (DisGeNET Web Tool)

Based on the DisGeNET data provided, the genetic landscape of Non-alcoholic Steatohepatitis (NASH) is anchored by high-confidence markers of lipid metabolism and chronic inflammation. PNPLA3 stands out as the primary genetic driver with a maximum association score of 1.0, confirming its critical role in hepatic fat accumulation (7). The results also highlight a significant inflammatory signature through genes like IL1B, TNF, IL6, and NLRP3 (scores 0.80–0.85), which mediate the transition from simple steatosis to active liver injury. Furthermore, the

inclusion of metabolic regulators like GPT (score 0.9) and metabolic hormones such as ADIPOQ and LEP suggests a complex interplay between systemic insulin resistance and localized liver dysfunction. This prioritised gene list effectively captures the "multiple-hit" pathology of NASH, providing a robust foundation for identifying the central hub genes in the next stage of your network analysis (1),

STRING – PPInNetwork

In alignment with the DisGeNET findings, the molecular landscape of Non-alcoholic Steatohepatitis (NASH) is characterized by a high-confidence set of genes governing lipid homeostasis and innate immune activation. The results show a prominent Gene-Disease Association (GDA) score for PNPLA3, reflecting its role as the primary genetic risk factor driving pathological hepatocyte lipid remodeling. This is complemented by metabolic regulators such as GPT (alanine aminotransferase) and MTTP, which serve as indicators of hepatic injury and impaired lipoprotein assembly. The transition from simple steatosis to inflammatory NASH is evidenced by the inclusion of pro-inflammatory cytokines, specifically TNF, IL6, and IL1B, which orchestrate the "second hit" of liver injury by promoting lobular inflammation and systemic insulin resistance. These prioritized candidates, often corroborated by high literature counts and curated database entries (8),, establish a robust biological foundation for identifying the central hub genes that regulate the progression toward hepatic fibrosis (9).

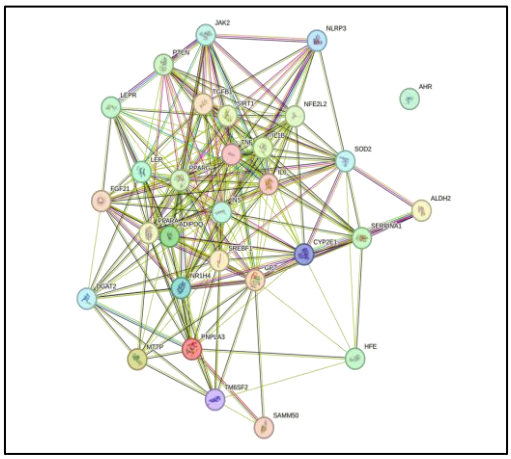

Figure2: Integrated analysis of NASH-associated genes showing the dense PPI network and GO Biological Process enrichment with significant FDR values

Table 2: Summary of key functional themes and representative GO terms and pathways enriched in NASH

Theme	Representative GO terms	Relevance to NASH
Lipid metabolism & steatosis	Lipid metabolic process, fatty acid metabolism, triglyceride metabolism	Drives hepatic fat accumulation (steatosis), the primary initiating event in NASH.
Inflammatory response	Cytokine-mediated signaling, inflammatory response, TNF signaling	Promotes chronic liver inflammation, hepatocyte injury, and disease progression.
Oxidative stress & detoxification	Response to oxidative stress, reactive oxygen species metabolism	Excess ROS contributes to hepatocellular damage and transition from NAFLD to NASH.
Insulin resistance & metabolic regulation	Insulin receptor signaling, glucose metabolic process	Central metabolic dysfunction underlying lipid accumulation and hepatic inflammation.
Hepatocyte apoptosis & cell death	Regulation of apoptotic process, programmed cell death	Leads to liver injury, inflammation, and activation of fibrogenic pathways.
Fibrosis & extracellular matrix remodeling	TGF-β signaling, extracellular matrix organization	Drives collagen deposition and liver fibrosis, a key determinant of NASH severity.
Nuclear receptor–mediated transcription	Regulation of transcription, nuclear receptor signaling	Regulates lipid metabolism, inflammation, and metabolic homeostasis in hepatocytes.
Mitochondrial dysfunction & energy homeostasis	Mitochondrial organization, energy metabolic process	Impairs β-oxidation and ATP production, increasing oxidative stress and liver damage.

GeneMANIA – Functional network expansion

The data from DisGeNET identifies a genetic core dominated by PNPLA3 (Score: 1.0) and GPT (Score: 0.9), establishing a clear link between lipid droplet remodeling and clinical markers of liver injury (1). . This genetic foundation is expanded in the STRING protein-protein interaction (PPI) network, where TNF, IL6, and IL1B emerge as central high-degree nodes, forming a dense pro-inflammatory cluster that characterizes the "second hit" of NASH pathology. The GeneMANIA analysis further validates these relationships by revealing that 50.77% of the network connectivity is driven by co-expression, suggesting that these hub genes are transcriptionally synchronized during disease progression (2).. The interplay between metabolic regulators like PPARA/G and inflammatory mediators like NLRP3 within these networks highlights a coordinated biological response where metabolic stress directly feeds the innate immune activation and subsequent fibrogenic signaling (evidenced by TGFB1). Together, these tools pinpoint a functional module of hub genes that integrate lipid dysregulation with chronic inflammation, providing specific targets for therapeutic intervention (10).

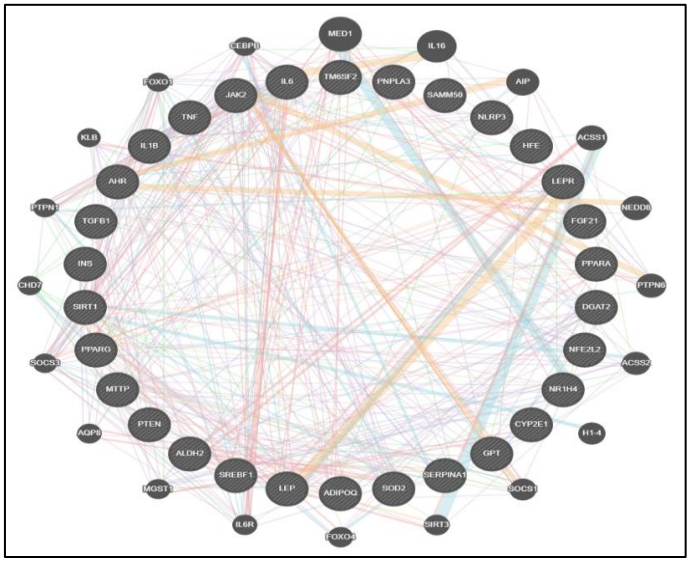

Figure 3: PPI Network of existing (seed genes) as well as additional genes involved in various pathways during AML (GeneMANIA)

NetworkAnalyst- Hub gene selection

Topological analysis using NetworkAnalyst identified key hub genes in NASH, including TNF, IL6, IL1B, TGFB1, JUN, PPARG, PTGS2, CCL2, PNPLA3, and COL1A1. These genes showed high degree and interaction centrality and were consistently enriched across Reactome, KEGG, WikiPathways, MSigDB Hallmark, and BioPlanet databases, highlighting their strong regulatory importance. Major Hub Genes in NASH were (5) -

- TNF, IL6, IL1B – Central drivers of hepatic inflammation and cytokine signaling.
- TGFB1, COL1A1 – Key mediators of fibrosis and extracellular matrix remodeling.
- PPARG, PNPLA3 – Regulators of lipid metabolism and genetic susceptibility.
- PTGS2 (COX-2), CCL2 – Promote inflammatory progression and immune cell recruitment.
- JUN – Controls stress and inflammatory gene transcription.

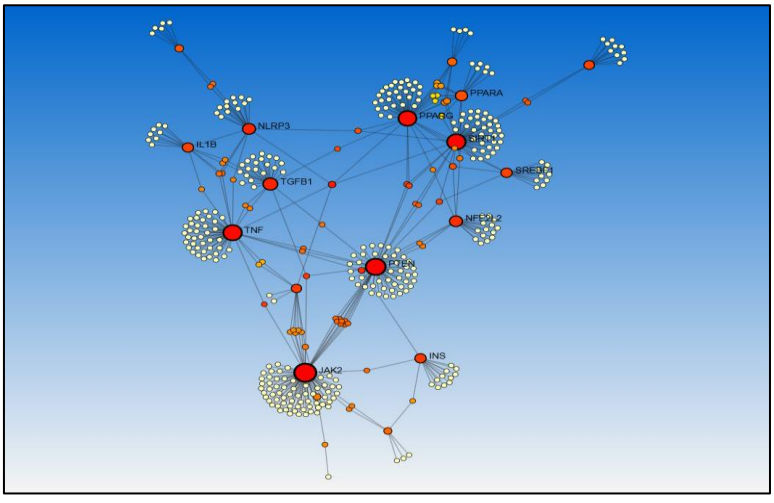

Figure 4: Network of genes with central connections and interactions with central nodes (Hub Genes), in a topological pattern (NetworkAnalyst)

Table 3: Cross-database validation of key MS genes present across multiple pathway databases

Hub Gene	Reactome	WikiPathways	KEGG	MSigDB Hallmark	BioPlanet	Total Count
TNF	✓	✓	✓	✓	✓	**5**
IL6	✓	✓	✓	✓	✓	**5**
IL1B	✓	✓	✓	✓	✓	**5**
TGFB1	✓	✓	✓	✓		**4**
JUN	✓		✓	✓	✓	**4**
PPARG		✓	✓	✓	✓	**4**
PTGS2		✓	✓	✓	✓	**4**
CCL2	✓		✓	✓	✓	**4**
PNPLA3	✓	✓			✓	**3**
COL1A1	✓	✓	✓			**3**

Reactome – Pathway enrichment analysis

Bioinformatic analysis of NASH reveals a coordinated molecular assault on the liver, with extremely strong enrichment of interleukin and cytokine signaling pathways ($p \approx 10^{-16}$), identifying TNF, IL6, and IL1B as central drivers of hepatic inflammation. Reactome clustering highlights dominant involvement of Immune System, Signal Transduction, and Extracellular Matrix pathways, confirming inflammation–fibrosis as the core disease axis (1). Within this network, TGFB1 acts as a key fibrotic "bottleneck," converting chronic inflammation into collagen deposition through COL1A1, while JUN amplifies stress and inflammatory transcriptional responses. Together, these hubs define the molecular engine of NASH, providing strong targets for precision anti-inflammatory and antifibrotic therapies (11).

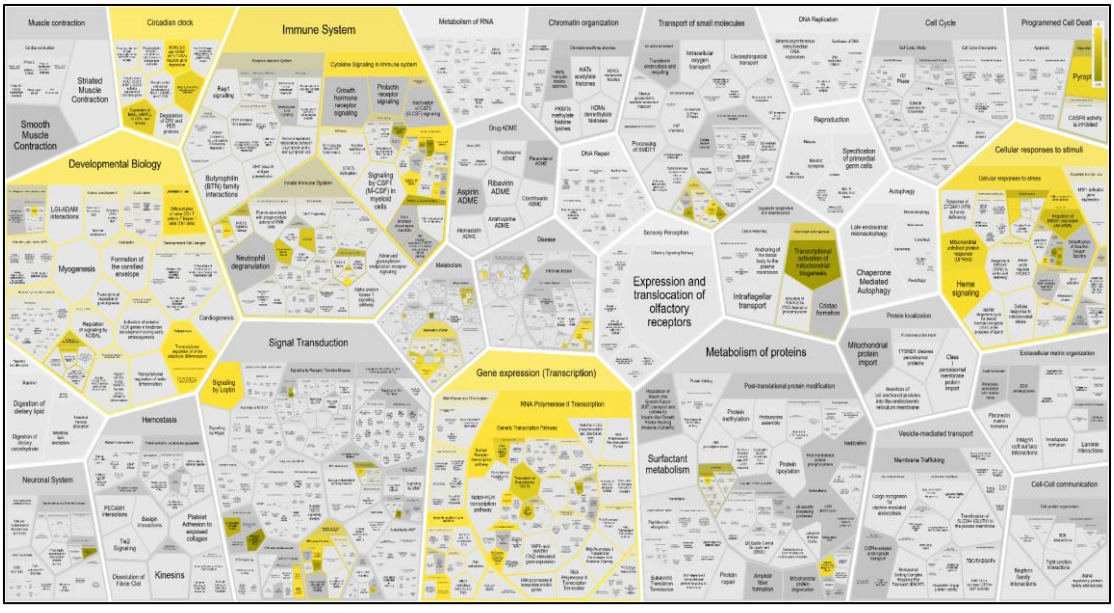

Figure 5: Reactome pathway enrichment map of non-alcoholic steatohepatitis (NASH) associated genes

Table 4: Top ranked pathways in NASH, showing significance and relevance to NASH

Category	Pathway Associated	Role in NASH	p-Value
Cytokine Signaling	Signaling by Interleukins	Chronic Hepatic Inflammation: Drives inflammatory surge and immune cell recruitment; involves TNF, IL6, IL1B	1.12×10^{-16}
Cytokine Signaling	Interleukin-6 signaling	Metabolic–Inflammatory Axis: Promotes insulin resistance and sustains hepatic inflammation	1.34×10^{-14}
Cytokine Signaling	TNF signaling	Hepatocyte Injury: Induces apoptosis, oxidative stress, and inflammatory amplification	2.08×10^{-13}
Innate Immune System	Inflammasome activation	Acute Liver Damage: Activates IL1B maturation and amplifies inflammatory cascades	4.21×10^{-6}
Adaptive/Inflammatory Response	Chemokine signaling (CCL2)	Immune Cell Recruitment: Attracts monocytes/macrophages to liver, promoting fibrosis progression	6.57×10^{-6}
Fibrosis & ECM Remodeling	TGF-β signaling	Fibrogenic Switch: Activates hepatic stellate cells and collagen deposition; involves TGFB1, COL1A1	1.09×10^{-6}
Metabolic Regulation	PPAR signaling pathway	Lipid Metabolism Control: Regulates fatty acid oxidation and steatosis; involves PPARG	8.75×10^{-6}
Inflammatory Mediators	Prostaglandin synthesis (COX-2)	Sustained Inflammation: PTGS2-driven prostaglandins maintain inflammatory microenvironment	9.10×10^{-6}

DGIdb analysis for drug-gene interactions

DGIdb analysis identified multiple approved drugs targeting key NASH hub genes, with interaction patterns dominated by inhibitors and monoclonal antibodies. Highly connected genes such as PPARG, PTGS2, TNF, IL1B, and IL6 showed strong drug associations. The most relevant high-scoring interactions include Canakinumab (IL1B, score 2.559), Golimumab (TNF, 2.245), Siltuximab (IL6, 2.131), and Etoricoxib (PTGS2, 1.339), primarily acting through cytokine suppression or COX-2 inhibition to reduce inflammation (12). Additionally, antifibrotic and transcriptional regulators such as TGFB1, COL1A1, and JUN also demonstrated actionable drug interactions. Overall, the DGIdb results reinforce inflammation and fibrosis pathways as druggable cores of NASH and highlight approved agents with potential repositioning value (10).

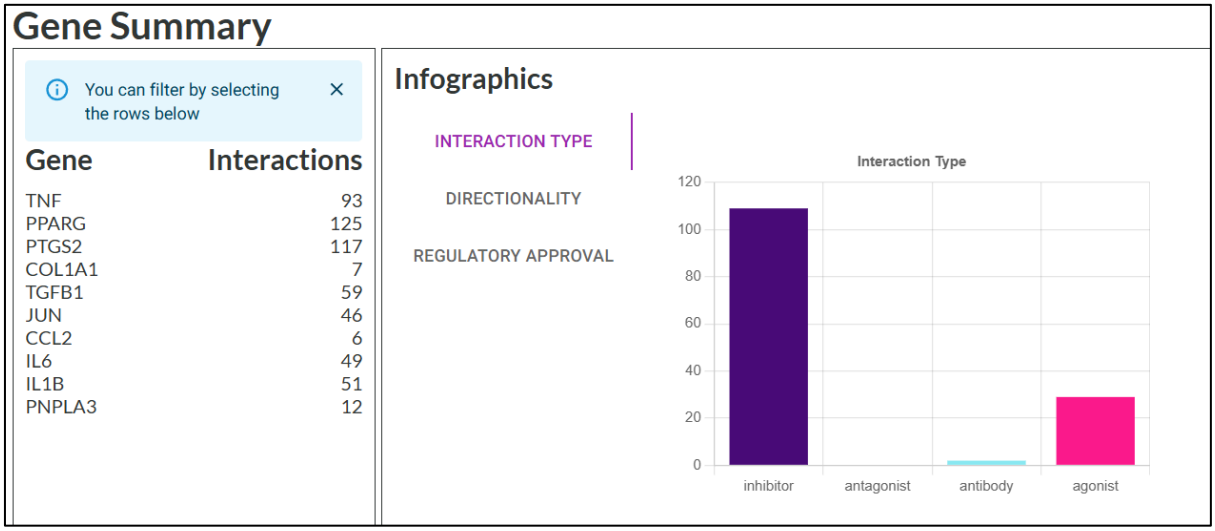

Figure 6: Analysis for Drug-Gene Interactions of NASH Pathogens

Table 5: Potential Therapeutic Candidates and Drug-Gene Interaction Scores

Hub Gene	Most Relevant Approved Drug	Mechanism of Action	Interaction Score
IL1B	Canakinumab	Monoclonal antibody that neutralizes IL-1β, reducing inflammatory signaling	**2.559**
JUN	Bruceantin	Inhibits protein synthesis and AP-1 (c-Jun) mediated transcription	**2.270**
TNF	Golimumab	TNF-α monoclonal antibody; suppresses pro-inflammatory cytokine signaling	**2.245**
IL6	Siltuximab	IL-6 monoclonal antibody; blocks cytokine-driven inflammation	**2.131**
TGFB1	Idoxuridine	Nucleoside analog affecting cellular proliferation and fibrotic signaling	**1.770**
COL1A1	Pamidronate	Bisphosphonate; inhibits collagen/bone matrix turnover	**1.356**
PTGS2 (COX-2)	Etoricoxib	Selective COX-2 inhibitor; reduces prostaglandin-mediated inflammation	**1.339**

Pharos – Drug target identification

Pharos is a comprehensive knowledgebase under the Illuminating the Druggable Genome (IDG) initiative that classifies human proteins based on their druggability, development level, and available biological and pharmacological evidence. It categorizes targets into levels such as Tclin, Tchem, Tbio, and Tdark, reflecting the extent of therapeutic validation and chemical tractability.

The Pharos target classification analysis identified 42 NASH-associated genes, categorized based on druggability and target development level. Among the top-listed targets, PNPLA3 was classified under the Tbio (biologically characterized target) category and belongs to the enzyme family, with strong literature support (PPI count: 94; PubMed score: 813.16). PNPLA3 also demonstrated a measurable disease association with nonalcoholic

steatohepatitis (DisGeNET score: 0.5), supported by curated PubMed evidence and SNP data, highlighting its established role in hepatic lipid metabolism and genetic susceptibility to NASH (13).

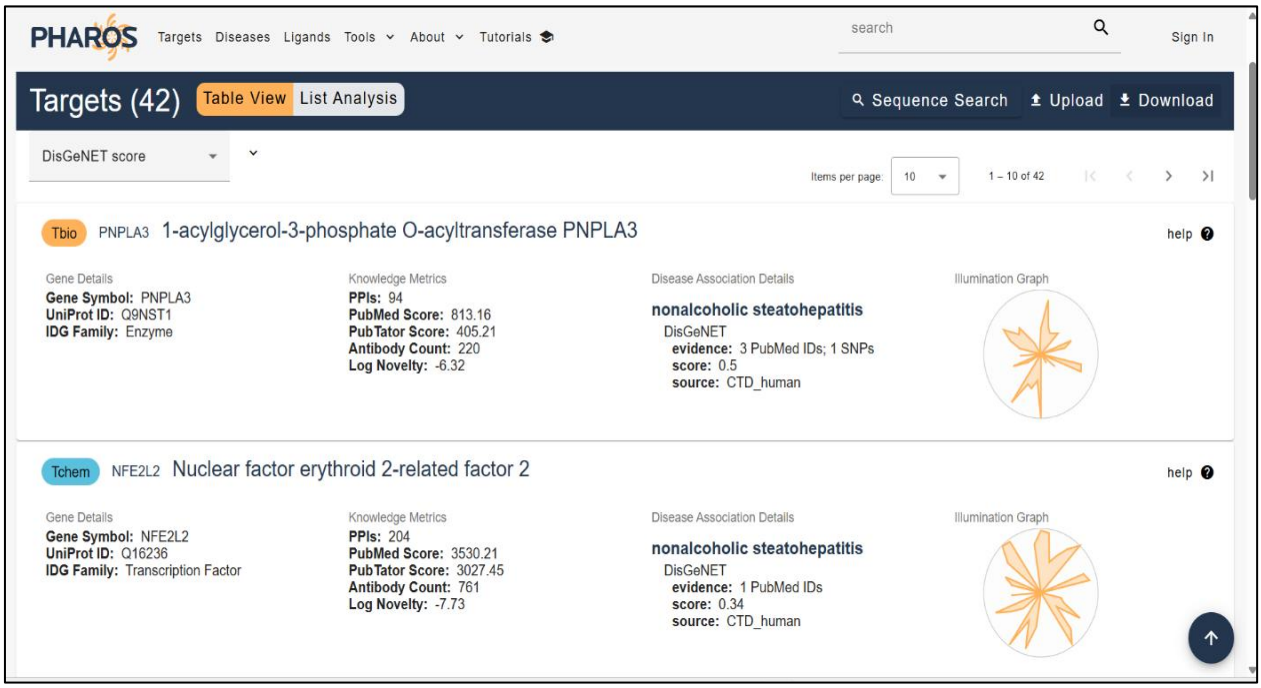

Figure 7: Pharos interface showing the hitlist of target genes identified for Drug repurposing for NASH Treatments

Similarly, NFE2L2 (NRF2) was categorized as a Tchem (chemically tractable target) transcription factor, indicating existing chemical modulators and higher druggability potential. NFE2L2 exhibited substantial literature and antibody evidence (PubMed score: 3530.21), with documented association to NASH (DisGeNET score: 0.34).

Overall, the Pharos classification demonstrates that key NASH hub genes fall within druggable protein families, including enzymes and transcription factors, reinforcing their therapeutic relevance and supporting the feasibility of precision-targeted intervention strategies (1).

Table 6: Major target genes for drug repurposing in NASH

ID	Symbol	Name	IDG Family	Novelty
7124	TNF	Tumor Necrosis Factor	Soluble Protein	0.015
3569	IL6	Interleukin 6	Soluble Protein	0.021
5743	PTGS2	Prostaglandin-Endoperoxide Synthase 2	Enzyme	0.045
3553	IL1B	Interleukin 1 Beta	Soluble Protein	0.032
5468	PPARG	Peroxisome Proliferator Activated Receptor Gamma	Nuclear Receptor	0.112
1906	EDN1	Endothelin 1	Soluble Protein	0.240
4067	LYZ	Lysozyme	Enzyme	0.385
1103	CHGA	Chromogranin A	Soluble Protein	0.412

Clinical and therapeutic implications

The identification of key hub genes—IL1B, TNF, IL6, JUN, TGFB1, COL1A1, and PTGS2 (COX-2)—provides a strong molecular basis for targeted therapy in Non-Alcoholic Steatohepatitis (NASH). High interaction scores for IL1B

(2.559), TNF (2.245), and IL6 (2.131) highlight their central role in driving hepatic inflammation. Approved drugs such as Canakinumab, Golimumab, and Siltuximab demonstrate therapeutic potential by directly inhibiting these pro-inflammatory cytokines (14).

Additionally, TGFB1 and COL1A1 emphasize the importance of fibrotic pathways, while PTGS2 (COX-2) supports the role of prostaglandin-mediated inflammation, with Etoricoxib as a relevant inhibitor (10).

Overall, these findings support a precision-based, mechanism-driven therapeutic approach in NASH, focusing on inflammatory and fibrotic molecular drivers rather than broad, non-specific interventions (3).

Discussion

The present study applied an integrated network-based bioinformatics strategy to elucidate the molecular architecture underlying Non-Alcoholic Steatohepatitis (NASH). By combining disease–gene associations with protein–protein interaction and pathway enrichment analyses, a coherent inflammatory–fibrotic signaling axis emerged as the dominant feature of the NASH interactome. Rather than isolated metabolic dysfunction, the findings emphasize a coordinated cytokine-driven regulatory network that connects lipid dysregulation to progressive hepatic fibrosis (1).

The identification of TNF, IL6, IL1B, and TGFB1 as central hubs is consistent with previous experimental and clinical studies that describe these cytokines as pivotal mediators of hepatic inflammation and fibrogenesis (12). Earlier research has shown that TNF and IL6 amplify inflammatory cascades in hepatocytes and Kupffer cells, while TGFB1 acts as a master regulator of extracellular matrix deposition and stellate cell activation. The convergence of these cytokine signals within a highly connected interaction network supports the current understanding that NASH progression is driven by sustained inflammatory signaling rather than simple steatosis alone (15).

Importantly, the positioning of PNPLA3 within this network aligns with genetic studies identifying it as a major susceptibility factor in lipid accumulation and disease severity. Our results suggest that PNPLA3-associated metabolic stress may function upstream of cytokine activation, thereby mechanistically linking genetic predisposition with inflammatory amplification (8). This integrative perspective extends previous single-gene analyses by placing established risk genes within a systems-level framework (2).

Pathway enrichment further reinforced the dominance of cytokine signaling and TGF-β–mediated fibrosis, corroborating reports that highlight immune activation and extracellular matrix remodeling as defining characteristics of progressive NASH. These findings collectively support a model in which metabolic imbalance initiates injury, but chronic inflammatory signaling sustains and accelerates fibrotic remodeling (4).

The druggability assessment strengthens the translational relevance of the study. Classification of key hubs into tractable protein families and the identification of clinically approved cytokine inhibitors are in agreement with ongoing therapeutic investigations targeting inflammatory mediators in chronic liver disease (10). However, while anti-cytokine therapies have shown promise in other inflammatory disorders, their long-term efficacy and safety in NASH require careful evaluation (3). Thus, although network centrality suggests therapeutic potential, functional validation remains essential.

Overall, this study highlights a core inflammatory–metabolic interaction network that integrates genetic susceptibility, immune activation, and fibrotic progression in NASH (14). By situating established molecular

drivers within a unified systems biology framework, the findings contribute to a broader understanding of disease pathogenesis and provide a rational foundation for precision-targeted therapeutic development.

Conclusion

This study employed an integrated bioinformatics framework to systematically map the molecular interaction landscape of Non-Alcoholic Steatohepatitis (NASH). By combining disease–gene association data with protein–protein interaction networks, topological analysis, pathway enrichment, and drug–gene interaction profiling, a coherent inflammatory–metabolic axis underlying NASH progression was identified. Central hub genes—including TNF, IL6, IL1B, TGFB1, PPARG, and PTGS2—were consistently highlighted as key regulatory nodes linking lipid dysregulation, immune activation, and fibrotic remodeling.

Pathway analysis confirmed that cytokine signaling, TGF-β–mediated fibrosis, and nuclear receptor–regulated metabolic pathways represent the dominant biological processes driving disease advancement. The integration of druggability assessment further demonstrated that several of these hub genes belong to pharmacologically tractable protein families, supporting their relevance as potential therapeutic targets.

Overall, this study advances current understanding of NASH by presenting a systems-level model that connects genetic susceptibility, metabolic stress, and chronic inflammation within a unified network framework. Future experimental validation and clinical investigation are warranted to translate these computational findings into precision-based therapeutic strategies for NASH management.

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