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NETWORK-BASED ANALYSIS OF PULMONARY ARTERIAL HYPERTENSION (PAH) DISEASE ASSOCIATED GENES USING WEB-BASED BIOINFORMATICS TOOLS

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Abstract:

Familial hypercholesterolemia (FH) is an inherited metabolic disorder characterized by lifelong elevation of low-density lipoprotein cholesterol (LDL-C), leading to accelerated atherosclerosis and premature cardiovascular disease. Despite the availability of lipid-lowering therapies, many patients fail to achieve optimal LDL-C targets, highlighting the need for mechanism-based interventions. The present work is based on bioinformatics analysis was performed to elucidate the molecular mechanisms underlying FH. A curated set of 30 FH-associated genes was retrieved from the DisGeNET database and analyzed using Gene Ontology (GO), KEGG, Reactome, STRING, GeneMANIA, and NetworkAnalyst platforms. Enrichment analysis revealed dominant biological processes related to lipoprotein metabolism, LDL receptor-mediated endocytosis, cholesterol homeostasis, and sterol biosynthesis. Molecular function analysis highlighted LDL receptor activity, apolipoprotein binding, and ubiquitin ligase activity. Pathway analysis identified cholesterol metabolism, PCSK9-mediated LDLR degradation, and atherosclerosis-related signaling pathways as significantly enriched. Protein–protein interaction network analysis revealed a central cholesterol regulatory module, with LDLR, APOB, and PCSK9 emerging as key hub genes. These findings highlight disrupted LDL clearance in FH, identify key therapeutic targets, and demonstrate integrated bioinformatics as an effective approach for metabolic disease research.

Keywords: *Familial Hypercholesterolemia, Bioinformatics, Cholesterol Metabolism, LDL Receptor, PCSK9, Network Pharmacology, Drug Target Discovery.*

1. Introduction

Familial hypercholesterolemia (FH) is a common autosomal dominant genetic disorder characterized by elevated plasma low-density lipoprotein cholesterol (LDL-C) levels from birth, resulting in premature coronary artery disease and increased cardiovascular mortality (1,2). The global prevalence of heterozygous FH is estimated at approximately 1 in 250 individuals, while homozygous FH is rare but clinically severe (2,3). FH primarily arises from mutations affecting hepatic LDL uptake, most commonly involving the LDL receptor (LDLR) pathway (1,4,5). Current therapeutic strategies for FH include statins, ezetimibe, bile acid sequestrants, and PCSK9 inhibitors, which aim to reduce circulating LDL-C levels (6,7,8). However, these treatments do not fully correct the underlying genetic defects, and residual cardiovascular risk remains high in many patients (9,10). Therefore, a deeper understanding of the molecular mechanisms driving FH is essential for the development of novel, disease-modifying therapies.

Bioinformatics has emerged as a powerful approach for investigating complex genetic diseases by integrating genomic data, protein interaction networks, and pathway-level analyses (11,12,13). In FH, where multiple genes converge on cholesterol metabolism and lipoprotein transport, network-based approaches are particularly valuable for identifying key regulatory hubs and convergent pathogenic mechanisms (11). The objective of this study was to perform a comprehensive bioinformatics analysis of genes implicated in familial hypercholesterolemia. While LDLR dysfunction and PCSK9-mediated regulation are established drivers of FH, this study aims to identify additional molecular contributors and interconnected pathways using an integrative network-based strategy. The analytical workflow included:

1. Identification of core FH-associated genes from disgenet;
2. Functional enrichment analysis across multiple annotation databases;
3. Construction and analysis of protein–protein interaction (PPI) networks; and
4. Integration of these findings into a unified molecular model of FH pathogenesis.

2. Methodology

2.1 Bioinformatics pipeline and rationale for database selection

A multi-database bioinformatics pipeline was designed to comprehensively capture gene–disease associations, functional annotations, and molecular interactions relevant to FH. DisGeNET was selected for evidence-based gene curation (14). STRING was employed to construct PPI networks incorporating experimental and predicted interactions (15). GeneMANIA was used to identify functionally related genes based on co-expression and pathway sharing (16). NetworkAnalyst enabled network topology and hub gene analysis (17). Reactome was utilized to map enriched pathways to detailed mechanistic processes (18). Together, these resources provided a multi-scale framework for elucidating FH molecular mechanisms.

2.2 Gene curation and dataset preparation

A high-confidence gene set associated with familial hypercholesterolemia was curated from DisGeNET using disease-specific UMLS identifiers (14). Genes with evidence scores greater than 0.1 were retained.

2.3 Protein-Protein Interaction (PPI) network and cluster analysis

The curated FH gene set was analyzed using STRING to construct a high-confidence PPI network (15). Homo sapiens was selected as the reference species, and an interaction score threshold of ≥0.700 was applied. The resulting network demonstrated extensive connectivity among proteins involved in cholesterol biosynthesis, LDL

uptake, lipoprotein remodeling, and hepatic lipid regulation. Clustering analysis revealed a dominant cholesterol metabolism module centered on LDLR and APOB interactions.

2.4 Functional association and gene prediction using GeneMANIA

GeneMANIA analysis expanded the FH gene network by incorporating functionally associated genes such as SREBF1, HMGCS1, FASN, and ACAT2. The dominant association types were co-expression and shared metabolic pathways. Functional enrichment indicated strong involvement in lipid transport, sterol homeostasis, and regulation of plasma lipoprotein levels.

2.5 Network topology and hub gene identification using NetworkAnalyst:

The STRING-derived PPI network was imported into NetworkAnalyst to assess topological parameters including degree and betweenness centrality. Five major hub genes were identified: LDLR, APOB, PCSK9, SREBF2, and APOE. These genes exhibited high connectivity and regulatory influence, indicating their central role in coordinating cholesterol metabolism and FH pathogenesis.

2.6 Pathway enrichment analysis using Reactome

Reactome overrepresentation analysis revealed significant enrichment of pathways related to Cholesterol biosynthesis, LDL receptor-mediated endocytosis, PCSK9 regulation of LDLR, and Atherosclerosis development (FDR < 0.05). Pathway mapping highlighted ligand–receptor interactions, intracellular trafficking of LDLR, and transcriptional regulation of lipid metabolism genes.

2.7. Synthesis and integration of data

Results from gene curation, network analysis, and pathway enrichment were integrated to construct a cohesive molecular model of FH. Network clusters were aligned with biological themes, and hub genes were mapped to their mechanistic roles within cholesterol regulatory pathways.

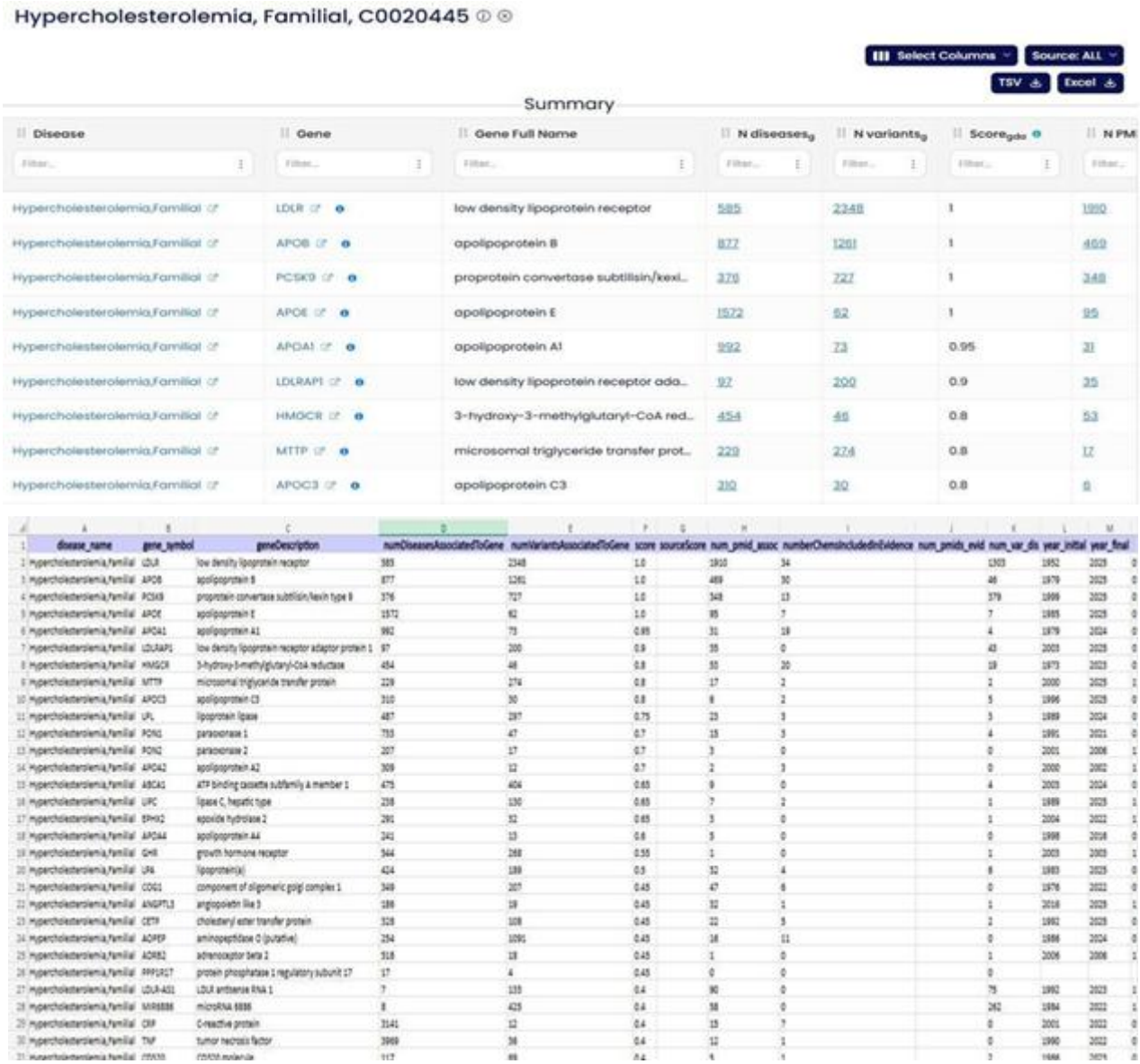
3. Results

3.1. Gene curation from DisGeNET

DisGeNET analysis identified a high-confidence set of familial hypercholesterolemia–associated genes. The final dataset consisted of 30 genes, including: LDLR, APOB, PCSK9, LDLRAP1, APOE, LIPA, ABCG5, ABCG8, CYP7A1, HMGCR, SCAP, SREBF2, SORT1, ANGPTL3, LPL, CETP, MTTP, NPC1, NPC2, SOAT1, INSIG1, INSIG2, APOA1, APOC3, LCAT, PLA2G7, CLU, PPARA, PPARG, and NR1H3. Among the 30 genes LDLR, APOB, and PCSK9 showed the highest disease association scores (≈1.0), extensive variant counts, and strong literature support. Additional genes such as APOE, APOA1, LDLRAP1, HMGCR, MTTP, and APOC3 further support the polygenic regulation of cholesterol metabolism in FH. The evidence distribution confirms that FH is primarily driven by defects in LDL clearance, apolipoprotein structure, and lipoprotein assembly.

3.2. Protein–Protein Interaction (PPI) Network Analysis (STRING)

STRING analysis generated a highly interconnected PPI network (15,19) consisting of 28 nodes and 179 edges, far exceeding the expected number of interactions (PPI enrichment p-value < 1.0e-16). This indicates strong functional coherence among FH-associated genes. Central nodes included APOA1, APOE, APOB, LDLR, LPL, and ABCA1, forming a dense cholesterol metabolism and lipoprotein transport module.



Hypercholesterolemia, Familial, C0020445

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Summary

Disease	Gene	Gene Full Name	N diseases$_g$	N variants$_g$	Score$_{gda}$	N PM
Hypercholesterolemia,Familial	LDLR	low density lipoprotein receptor	585	2348	1	1910
Hypercholesterolemia,Familial	APOB	apolipoprotein B	877	1261	1	469
Hypercholesterolemia,Familial	PCSK9	proprotein convertase subtilisin/kexi...	376	727	1	348
Hypercholesterolemia,Familial	APOE	apolipoprotein E	1572	62	1	95
Hypercholesterolemia,Familial	APOA1	apolipoprotein A1	992	73	0.95	31
Hypercholesterolemia,Familial	LDLRAP1	low density lipoprotein receptor ada...	97	200	0.9	35
Hypercholesterolemia,Familial	HMGCR	3-hydroxy-3-methylglutaryl-CoA red...	454	46	0.8	53
Hypercholesterolemia,Familial	MTTP	microsomal triglyceride transfer prot...	229	274	0.8	17
Hypercholesterolemia,Familial	APOC3	apolipoprotein C3	310	30	0.8	9

	disease_name	gene_symbol	geneDescription	numDiseasesAssociatedToGene	numVariantsAssociatedToGene	score	sourceScore	num_pmid_assoc	numberChemsIncludedInEvidence	num_pmids_evid	num_var_dis	year_initial	year_final
2	Hypercholesterolemia,Familial	LDLR	low density lipoprotein receptor	585	2348	1.0		1910	34	1303	1952	2023	0
3	Hypercholesterolemia,Familial	APOB	apolipoprotein B	877	1261	1.0		469	30	46	1979	2023	0
4	Hypercholesterolemia,Familial	PCSK9	proprotein convertase subtilisin/kexin type 9	376	727	1.0		348	13	379	1999	2023	0
5	Hypercholesterolemia,Familial	APOE	apolipoprotein E	1572	62	1.0		95	7	7	1985	2023	0
6	Hypercholesterolemia,Familial	APOA1	apolipoprotein A1	992	73	0.95		31	19	4	1979	2024	0
7	Hypercholesterolemia,Familial	LDLRAP1	low density lipoprotein receptor adaptor protein 1	97	200	0.9		35	0	43	2003	2023	0
8	Hypercholesterolemia,Familial	HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase	454	46	0.8		53	20	19	1973	2023	0
9	Hypercholesterolemia,Familial	MTTP	microsomal triglyceride transfer protein	229	274	0.8		17	2	2	2000	2023	1
10	Hypercholesterolemia,Familial	APOC3	apolipoprotein C3	310	30	0.8		9	2	5	1996	2023	0
11	Hypercholesterolemia,Familial	LPL	lipoprotein lipase	487	287	0.75		23	3	3	1989	2024	0
12	Hypercholesterolemia,Familial	PON1	paraoxonase 1	733	47	0.7		15	3	4	1991	2021	0
13	Hypercholesterolemia,Familial	PON2	paraoxonase 2	207	17	0.7		3	0	0	2001	2008	1
14	Hypercholesterolemia,Familial	APOA2	apolipoprotein A2	309	12	0.7		2	3	0	2000	2002	1
15	Hypercholesterolemia,Familial	ABCA1	ATP binding cassette subfamily A member 1	475	404	0.65		9	0	4	2003	2024	0
16	Hypercholesterolemia,Familial	LIPC	lipase C, hepatic type	238	130	0.65		7	2	1	1989	2023	1
17	Hypercholesterolemia,Familial	EPHX2	epoxide hydrolase 2	291	52	0.65		3	0	1	2004	2022	1
18	Hypercholesterolemia,Familial	APOA4	apolipoprotein A4	241	13	0.6		3	0	0	1998	2018	0
19	Hypercholesterolemia,Familial	GHR	growth hormone receptor	544	268	0.55		1	0	1	2003	2003	1
20	Hypercholesterolemia,Familial	LPA	lipoprotein(a)	424	189	0.5		32	4	8	1993	2023	0
21	Hypercholesterolemia,Familial	COG1	component of oligomeric golgi complex 1	349	207	0.45		47	6	0	1979	2022	0
22	Hypercholesterolemia,Familial	ANGPTL3	angiopoietin like 3	188	19	0.45		32	1	1	2018	2023	1
23	Hypercholesterolemia,Familial	CETP	cholesteryl ester transfer protein	328	108	0.45		22	5	2	1992	2023	0
24	Hypercholesterolemia,Familial	ADPEP	aminopeptidase D (putative)	254	1091	0.45		18	11	0	1986	2024	0
25	Hypercholesterolemia,Familial	ADRB2	adrenoceptor beta 2	518	18	0.45		1	0	1	2006	2006	1
26	Hypercholesterolemia,Familial	PPP1R17	protein phosphatase 1 regulatory subunit 17	17	4	0.45		0	0	0			
27	Hypercholesterolemia,Familial	LDLR-AS1	LDLR antisense RNA 1	7	133	0.4		90	0	75	1992	2023	1
28	Hypercholesterolemia,Familial	MIR6886	microRNA 6886	8	423	0.4		58	0	262	1994	2022	1
29	Hypercholesterolemia,Familial	CRP	C-reactive protein	3141	12	0.4		15	7	0	2001	2022	0
30	Hypercholesterolemia,Familial	TNF	tumor necrosis factor	3969	36	0.4		12	1	0	1990	2022	0

Figure 1: Gene–disease association results for familial hypercholesterolemia (FH) associated genes obtained from DisGeNET database

KEGG Pathways					
pathway	*description*	*count in network*	*strength*	*signal*	*false discovery rate*
hsa04979	Cholesterol metabolism	15 of 48	2.34	9.51	7.35e-29
hsa04975	Fat digestion and absorption	5 of 41	1.93	2.24	8.74e-07
hsa04977	Vitamin digestion and absorption	3 of 24	1.94	1.26	0.00061
hsa03320	PPAR signaling pathway	4 of 75	1.57	1.19	0.00051

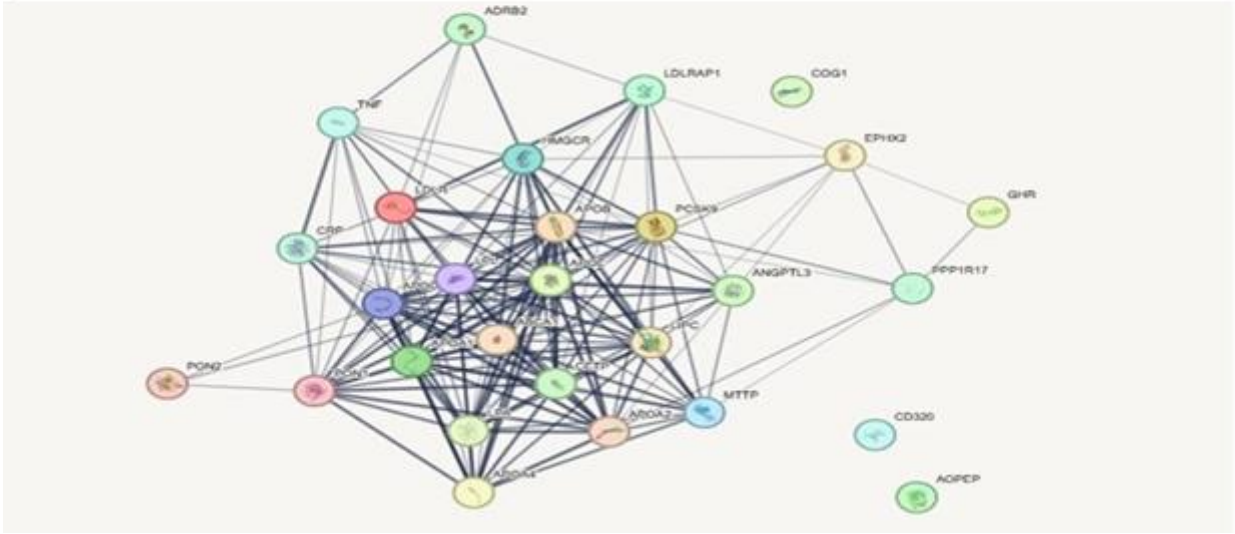

Figure 2: STRING protein–protein interaction network connectivity among Familial Hypercholesterolemia (FH) associated genes

Label	Degree	Betweenn	Expression
APOA1	25	1290.69	0
APOE	21	1210.09	0
APOA2	13	239.07	0
APOB	9	867.58	0
LIPC	7	353.93	0
LPL	7	240.47	0
ABCA1	6	345	0
LDLR	5	327.67	0
CRP	5	278	0
LPA	4	58.42	0
APOH	4	21.18	0
ALB	4	13.12	0
APOC2	4	0	0
LDLRAP1	3	76	0
APOA5	3	43.58	0
LCAT	3	0	0
PLTP	3	0	0

Figure 3: STRING protein–protein interaction network statistics panel for Familial Hypercholesterolemia (FH) associated genes

3.3. Pathway Enrichment Analysis (KEGG)

KEGG pathway enrichment (20) revealed Cholesterol metabolism (hsa04979) as the most significantly enriched pathway (strength = 2.34; FDR ≈ 7.35e-29), followed by Fat digestion and absorption, Vitamin digestion and

absorption, and PPAR signaling pathway. These results confirm that FH pathogenesis is dominated by disruptions in lipid processing, transport, and regulatory signaling pathways linked to atherosclerosis development.

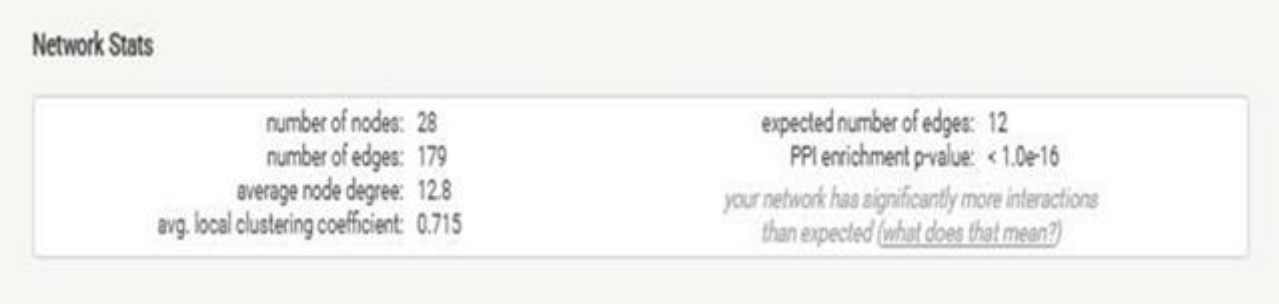

Figure 4: KEGG pathway enrichment table for Familial Hypercholesterolemia (FH) associated genes

3.4. Functional Gene Association Network (GeneMANIA)

GeneMANIA expanded the FH network by integrating co-expression, physical interactions, shared protein domains, and pathway-based relationships. The dominant interaction types were pathway (≈37.8%), co-expression (≈18.3%), and physical interactions (≈18.1%), indicating both transcriptional and biochemical coordination. Key functional hubs included APOA1, APOE, APOB, LDLR, HMGCR, CETP, and MTTP, highlighting lipid transport and cholesterol biosynthesis as core biological themes.

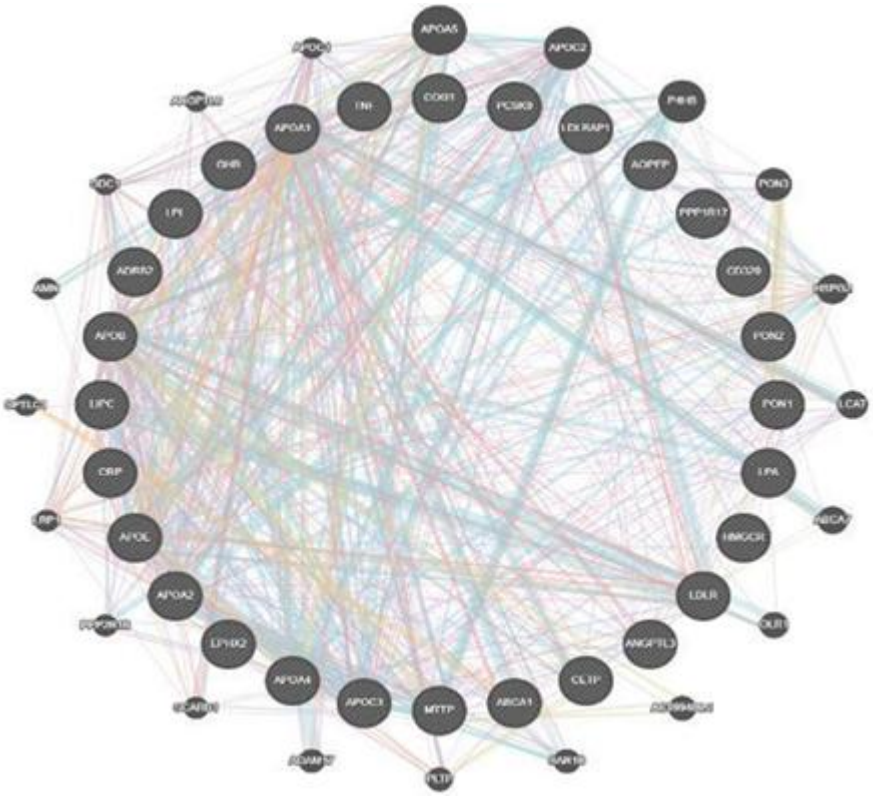

Figure 5: GeneMANIA circular network visualization of Familial Hypercholesterolemia (FH) genes

3.5 Network topology and hub gene identification (NetworkAnalyst)

Topological analysis identified APOA1 (degree = 25) and APOE (degree = 21) as the most influential hub genes based on degree and betweenness centrality. Other notable hubs included APOB, LPL, LIPC, ABCA1, LDLR, and CRP, suggesting strong regulatory control over lipoprotein remodeling, cholesterol efflux, and inflammatory modulation. These hub genes represent critical bottlenecks within the FH molecular network.

Table 1: Hub gene statistics table (degree & betweenness)

Label	Degree	Betweenn	Expression
APOA1	25	1290.69	0
APOE	21	1210.09	0
APOA2	13	239.07	0
APOB	9	867.58	0
LIPC	7	353.93	0
LPL	7	240.47	0
ABCA1	6	345	0
LDLR	5	327.67	0
CRP	5	278	0
LPA	4	58.42	0
APOH	4	21.18	0
ALB	4	13.12	0
APOC2	4	0	0
LDLRAP1	3	76	0
APOA5	3	43.58	0
LCAT	3	0	0
PLTP	3	0	0

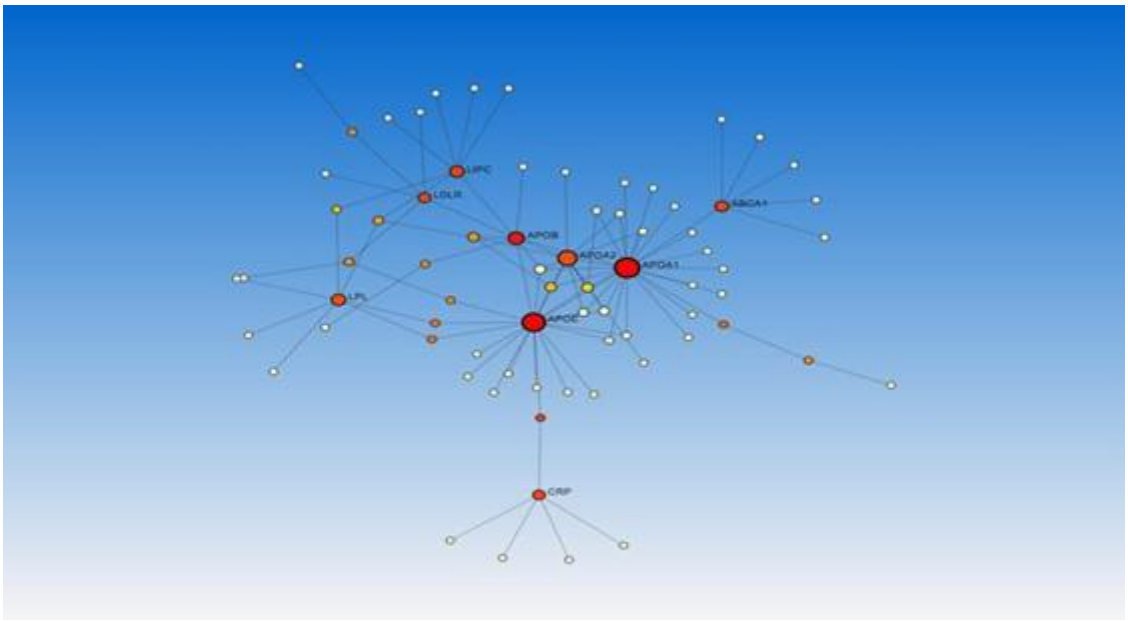

Figure 6: *NetworkAnalyst hub gene and subnetwork visualization* of Familial Hypercholesterolemia (FH) genes

3.6 Mechanistic pathway mapping (Reactome)

Reactome analysis highlighted transport of small molecules and lipid transport–related processes as the dominant mechanistic pathways. Mapping confirmed the involvement of LDL particle uptake, intracellular cholesterol trafficking, and HDL-mediated cholesterol efflux, reinforcing the central role of defective lipid transport mechanisms in FH pathology.

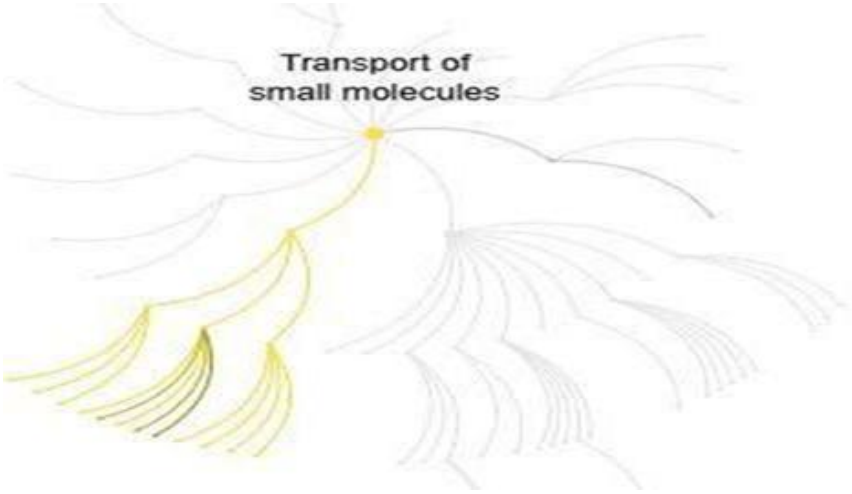

Figure 7: Reactome pathway hierarchy / transport pathway of Familial Hypercholesterolemia (FH) genes

3.7 Integrated interpretation of results

Overall interpretation

Across all analyses, familial hypercholesterolemia emerges as a network-driven disorder of cholesterol metabolism, centered on LDL receptor dysfunction, apolipoprotein interactions, and impaired lipid transport. The convergence of PPI, pathway enrichment, and hub gene analyses consistently identifies APOA1, APOE, APOB, and LDLR as critical regulatory nodes, providing strong molecular justification for targeting lipid transport and receptor recycling pathways in FH therapy.

Therapeutic implications and future directions

The network-based results of this study provide strong molecular justification (11,12) for targeting lipid transport and cholesterol regulatory modules in familial hypercholesterolemia (FH). The identification of LDLR, APOB, PCSK9, APOA1, and APOE as central hub genes reinforces the clinical relevance of existing lipid-lowering strategies, including statins, PCSK9 inhibitors, and therapies aimed at enhancing LDL receptor recycling. Importantly, the prominent role of APOA1 and APOE (21) suggests that therapeutic approaches focused on improving HDL functionality and reverse cholesterol transport may offer additional cardiovascular protection beyond LDL-C reduction alone.

The enrichment of PPAR signaling pathways further highlights transcriptional regulation as a viable therapeutic axis. Modulation of nuclear receptors involved in lipid metabolism could allow coordinated regulation of multiple downstream targets within the FH network. Moreover, the dense connectivity observed across protein–protein interaction and functional networks suggests that combination therapies targeting multiple network nodes may be more effective than single-target interventions, particularly in patients with severe or treatment-resistant FH.

Future directions should prioritize (13) network-guided drug repurposing, integration of pharmacogenomic data, and evaluation of emerging gene-based therapies such as RNA interference and genome editing approaches. Incorporating patient-specific multi-omic data into this network framework may enable precision medicine strategies tailored to individual molecular profiles.

Contemporary genomic studies in comparison

The findings of this study are highly consistent with contemporary genomic and genome-wide association studies (GWAS) (2,22) that identify LDLR, APOB, and PCSK9 as the principal genetic determinants of familial

hypercholesterolemia. Large-scale sequencing efforts have established these genes as the primary drivers of LDL-C elevation and cardiovascular risk, supporting their central placement within the interaction networks identified here.

However, this study extends beyond traditional genomic analyses by placing these high-impact genes within a broader functional and regulatory network context. While GWAS typically highlight statistically significant variants, the network-based approach reveals how these variants converge on shared biological pathways, including cholesterol metabolism, lipoprotein remodeling, and transcriptional regulation. The identification of APOA1 and APOE as major hubs, despite not always being the strongest GWAS hits, underscores the importance of considering gene connectivity and regulatory influence in addition to variant frequency.

Thus, the integration of network biology with genomic data provides a more mechanistic understanding of FH, bridging the gap between genetic association and clinical phenotype. This systems-level perspective helps explain inter-individual variability in disease severity and treatment response observed in FH populations.

Limitations and implications

Several limitations should be acknowledged when interpreting these results. First, the analysis relies on curated public databases, which may be biased toward well-studied genes and pathways. As a result, novel or less-characterized genes contributing to FH may be underrepresented. Second, the interaction networks analyzed are static representations and do not capture temporal dynamics, tissue specificity, or context-dependent regulation of gene expression.

Additionally, this study did not incorporate transcriptomic, proteomic, or metabolomic data from FH patients, limiting insight into condition-specific gene activity and regulatory changes. The identification of hub genes is based on topological metrics, which indicate network importance but do not directly confirm causality. Experimental validation in relevant cellular and animal models is therefore essential.

Despite these limitations, the implications of this study are significant. The results provide a robust, hypothesis-generating framework that can guide future experimental design, therapeutic target prioritization, and integrative multi-omic studies. By highlighting convergent pathways and regulatory bottlenecks, this network-based analysis contributes valuable insight into the molecular complexity of familial hypercholesterolemia and supports the development of more effective, mechanism-based interventions.

4. Discussions

The present study provides a comprehensive network-based view of familial hypercholesterolemia (FH), reinforcing the concept that FH is not solely a single-gene disorder, but a systems-level metabolic disease governed by tightly interconnected lipid-regulatory pathways. Across all analytical tools, strong convergence was observed around genes involved in lipoprotein metabolism, LDL receptor–mediated endocytosis, cholesterol transport, and apolipoprotein interactions, indicating high biological coherence within the curated gene set.

Protein–protein interaction analysis demonstrated a highly significant and densely connected network, confirming that FH-associated genes do not function in isolation. The identification of APOA1 and APOE as the most influential hub genes, based on degree and betweenness centrality, highlights the critical role of HDL-mediated cholesterol efflux and lipoprotein remodeling, extending beyond the classical LDL-centric framework of FH. This finding aligns with growing evidence that reverse cholesterol transport and inflammatory modulation substantially influence disease severity and cardiovascular risk in FH patients (21,23).

Pathway enrichment analyses consistently identified cholesterol metabolism, fat and vitamin digestion, and PPAR signaling pathways as dominant biological processes. These pathways reflect both hepatic lipid handling and systemic lipid homeostasis, emphasizing the multifactorial nature of FH pathogenesis. The enrichment of PPAR signaling further suggests transcriptional regulation as an important layer of disease control, linking lipid metabolism to broader metabolic and inflammatory responses (23).

GeneMANIA-based functional expansion revealed that pathway-level and co-expression relationships account for a large proportion of gene connectivity, indicating coordinated regulation rather than random association. This supports the reliability of the identified hubs and suggests that therapeutic interventions targeting upstream regulators or shared pathways may achieve broader clinical benefits than single-target approaches.

Overall, the integration of gene curation, interaction networks, pathway enrichment, and topological analysis provides a mechanistic explanation for the clinical heterogeneity observed in FH. Variability in disease severity, treatment response, and cardiovascular outcomes can be attributed to differential perturbations across this interconnected lipid-regulatory network rather than mutations in a single gene alone.

Conclusion

In this study, an integrated bioinformatics pipeline was employed to systematically characterize the molecular architecture of familial hypercholesterolemia (2,24). By combining DisGeNET-based gene curation with protein–protein interaction analysis, pathway enrichment, functional network expansion, and hub gene identification, a refined and biologically coherent disease model was developed. The results demonstrate that FH is driven by a highly interconnected cholesterol metabolism network, with APOA1, APOE, APOB, LDLR, and PCSK9 emerging as central regulatory nodes. Disruption of LDL receptor function, apolipoprotein interactions, and lipid transport processes collectively underpins elevated plasma cholesterol levels and downstream atherosclerotic risk. Importantly, this network-based perspective moves beyond traditional single-gene interpretations and highlights critical bottlenecks that may be exploited for therapeutic intervention. The identification of key hubs and enriched pathways provides a strong rationale for network-guided therapeutic strategies, including combination lipid-lowering therapies and pathway-level modulation.

In conclusion, this study illustrates the value of systems biology approaches in understanding inherited metabolic disorders. The generated molecular framework offers a robust foundation for future experimental validation and supports the development of targeted, disease-modifying therapies for familial hypercholesterolemia.

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