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SHARED GENETIC PATHWAYS IN HEPATITIS B/C AND CIRRHOSIS: A NETWORK-BASED GENE EXPRESSION ANALYSIS

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Abstract

Hepatitis B and C (HBV, HCV) are major global contributors to liver disease and often lead to cirrhosis. This study explored shared genetic features linking HBV/HCV infections to cirrhosis using a network-based analysis of gene expression data. Transcriptomic profiles from GEO datasets (GSE121248, GSE55092, GSE89377, GSE139602) were integrated, identifying 47 commonly upregulated genes associated with disease progression. Functional enrichment and pathway analysis were conducted using R, while a protein-protein interaction (PPI) network was constructed via the STRING plugin in Cytoscape. Ten hub genes (CDC20, CCNB2, MELK, AURKA, PRC1, TOP2A, CDCA5, PTTG1, TYMS, UBE2C) were identified as key modulators. Additional interaction networks–TF–miRNA and drug–gene–were developed using NetworkAnalyst. This systems biology approach highlights the molecular complexity underlying hepatitis-related cirrhosis and identifies candidate genes for potential therapeutic targeting, pending further validation.

INTRODUCTION

Hepatitis B and C viruses, or HBV and HCV, are a global public health emergency because they cause an alarming increase in the incidence of liver diseases, especially cirrhosis (Te and Jensen 2010). Liver scarring is a hallmark of cirrhosis, which may cause fatal complications such hepatocellular carcinoma and liver failure (Schuppan and Afdhal 2008). Researchers must dig deep into the origins of HBV and HCV infections and the progression of chronic liver disease because these viruses affect millions of people annually. The goal of this study is to get a better understanding of the genetic relationships between cirrhosis, hepatitis B and C virus (HBV) infection and HCV and HCV infection. In accordance with Breunig and Zlatanova (2011), we searched the Gene Expression Omnibus (GEO) database for gene expression datasets using a network-based approach. Liver tissues with infections or cirrhosis were analysed using four datasets: GSE121248, GSE55092, GSE89377 and GSE139602.

This research brought together various disease progression datasets to discover shared genes that the body activates during the disease process (Song, Su et al. 2019). They studied gene expression data to recognize how viral hepatitis leads to cirrhosis. Research proves that several internal actions exist between genetic signals and disease development because multiple health problems share the same genetic source. The research analysis identifies 47 genes that indicate increased activity. These crucial genes support important biological tasks like cell

control and immune response plus they act in inflammatory and scarring processes (Iizuka, Oka et al. 2003). Our next step must be to study these biological pathways because they show how liver tissue damage at the end leads to cirrhosis during viral infections.

The researchers further elucidated these gene relationships by using the R package to investigate the related pathways and gene ontologies (Petri, Jayaraman, et al. 2014). Insights were gained from this analysis into how certain genes will interact in biological networks and also how dysregulation of genes in specific patterns will further lead to disease progression. However, one of the significant improvements was in building a protein–protein interaction (PPI) network with the help of the STRING Cytoscape plugin (Menon and Elengoe 2020). The identified genes are networked to visualize their interactions in terms of proteins encoded by them and to find hub genes, meaning these genes are very highly connected within that network and so again should play crucial roles in disease processes.

From this PPI network, ten hub genes were CDC20, CCNB2, MELK, AURKA, PRC1, TOP2A, CDCA5, PTTG1, TYMS and UBE2C. It was found that these genes were crucial in regulating functions of the cell such as the cell cycle and DNA repair. Given that their upregulation was observed for both HBV and HCV infections, they have possible roles in the development of cirrhosis (Shackel, McGuinness et al. 2002). The identification of these hub genes will pave the way for the future research on these genes and therapeutic interventions if feasible. Targeting these key genes, it may be possible to come up with strategies to stop or reverse progression of liver disease in chronic HBV or HCV patients. The research emphasizes that an approach of systems biology, wherein the interactions among the biological system elements are taken into consideration rather than concentrating on single genes or pathways, is required.

The study also developed interaction networks of transcription factors (TFs), TFsmiRNA and drug interactions in the NetworkAnalyst platform (Basar, Hosen et al. 2023). This full analysis expands our perception of the regulatory networks formed in gene expression during hepatitis and cirrhosis. In detail, this research breaks Hepatitis B/C infections and cirrhosis down to a fine network based gene expression platform analysis uncovering the shared genetic aspects between these two disease conditions.

Material and Methods

2.1. Acquisition of datasets

Microarray gene expression profiles for cirrhosis (GSE89377 & GSE139602) and hepatitis B/C (GSE55092) were obtained from the Gene Expression Omnibus (GEO). (https://www.ncbi.nlm.nih.gov/gds). Both databases centre on peripheral blood cells. The datasets GSE121248 and GSE55092 were processed using the GPL26963 platform. The sample pool consisted of 10 people: 5 with mild cirrhosis, 5 with severe hepatitis B/C and 5 healthy controls. A human lncRNA V5 microarray, model 085982, manufactured by Agilent, serves as the foundation. The GPL570 (Affymetrix Human Genome U133 plus 2.0 Array) platform was used to collect samples for the GSE18781 dataset from twelve persons with cirrhosis and twelve healthy controls.

2.2. Identification of common upregulated genes

To find shared differentially expressed genes (DEGs) across the two sets of data, GEO2R https://www.ncbi.nlm.nih.gov/geo/geo2r/ was done. According to Sui, Li et al. (2023), GEO2R can identify DEGs by comparing several datasets and then using the GEOquery and limma R tools developed by the Bioconductor project. According to Ferreira and Zwinderman (2006), the false discovery rate was limited using Benjamini-Hochberg. Once received via GEO2R in table format, the shared DEGs from both datasets were imported into RStudio for further analysis. Filtering datasets was done by setting adjusted p-values to less than 0.01 and log2-fold changes to less than -1. A Venn diagram was created using Bioinformatics and Evolutionary Genomics. http://bioinformatics.psb.ugent.be/webtools/Venn/ web-based instrument and then to get often elevated genes.

2.3. Enrichment analysis of common upregulated genes

One way to evaluate the collective behaviours of genes in connection to health and disease is via gene set enrichment analysis, which was described by Hong,

Zhang et al. (2014). For genes that were raised often, Enrichr was used to get gene ontologies (GO) and associated pathways. (https://maayanlab.cloud/Enrichr/).
Khan, Dębski and colleagues (2016) state that Enrichr has several collective gene list features and is an easy-to-use web-based application for enrichment analysis. For pathways analysis, KEGG, BioPlanet, Reactome and MSigDB were used.

2.4. Network analysis
An essential part of system biology is network analysis, which helps us understand how proteins interact at the cellular and molecular levels (Hevey 2018). Research focused on networks, as opposed to individual genes, may also teach us a lot about gene sets. Our network construction tool of choice was the STRING protein quarry Cytoscape plugin. Gene interaction searches may be conducted in the STRING database. (https://string-db.org/)Used to describe the physical and functional links between proteins across more than 2000 species. With a confidence level of 0.400, we typed upregulated genes into the search box. We used Cytoscape and its associated plugin tools for viewing and customisation after the network retrieval (Smoot, Ono et al., 2011).

2.5. Hub genes identification and module analysis
In a network, there are several kinds of nodes and edges; genes with the most connections are known as hub genes. In many cases, the upkeep of biological activities depends on hub genes, which are more strongly connected. Our PPI network hub genes were located using cytoHubba, a Cytoscape plugin software. An easy-to-use program that provides eleven topological analysis methods for investigating critical nodes in biological networks is CytoHubba, claims Chin, Chen and colleagues (2014). This research made use of the degree topological method, which is based on the number of interactions between genes in the PPIs network. An additional Cytoscape plugin tool called Molecular Complex Detection (MCODE) was used to identify the tightly related parts of the PPIs network. Xu and Hejzlar (2008) state that MCODE streamlines visualisation by eliminating dense regions around a protein of interest.

2.6. Transcriptional factor regulatory network of hub genes
The transcription factor (TF) network is crucial for cell fate choices in mammals and for maintaining tissue homeostasis in adults, although it is often disrupted by illness (Lindemose, O'Shea et al. 2013). Using NetworkAnalyst, we built the network of interactions between hub genes and TFs.(https://www.networkanalyst.ca/NetworkAnalyst/uploads/ListUploadView.xht).
The comprehensive web-based platform NetworkAnalyst offers a visual network for the investigation of gene expression (Zhou, Soufan et al. 2019). To draw up the TFs gene interaction network, the JASPAR database was used. (http://jaspar.genereg.net/) which is included in NetworkAnalyst platform.

2.7. TFs-miRNA regulatory network analysis
According to Rad, Langroudi et al. (2015), TFs control transcription before it happens, while microRNAs control gene expression after transcription has already occurred. The TFsmiRNA regulatory network for hub genes was constructed using the RegNetwork repository and the NetworkAnalyst tool (Liu, Wu et al. 2015). A filter was applied to the network at the 1° cutoff level. Finally, the network that had been obtained from NetworkAnalyst was seen in Cytoscape.

2.8. Protein drug interaction network
We concluded by creating a drug interaction network for our hub genes to help find potential drugs for cirrhosis and hepatitis B/C. The network was built using DrugBank.(https://go.drugbank.com/)dataset using the web-based tool NetworkAnalyst (Knox, Wilson et al., 2024). Once the network file was retrieved from NetworkAnalyst, Cytoscape was used to display it.

Results
3.1. Identification of common upregulated genes between Hepatitis B/C and Cirrhosis:
We looked at two datasets, GSE121248 and GSE55092 and GSE89377 and GSE139602, to find common elevated genes between cirrhosis patients and hepatitis B/C patients. We were able to extract 47 frequently upregulated genes from these datasets.

1. These common upregulated genes were included as GPC3, SPINK1, AKR1B10, TOP2A, ACSL4, ASPM, CDKN3, SULT1C2, PRC1, SPP1, CD24, NQO1, CCNB2, S100P, CDC20, PTTG1, COL1A2, COL4A1, MELK, AURKA, LRRC1, DTNA, GMNN, UBE2C, THY1, AKR1C3, IFI27, TMEM45B, TYMS, MDK, FAT1, SORT1, IGSF3, ADGRG2, SLC51B, MUC13, CDCA5, S100A10, TGM3, FABP4, APOLD1, TSPAN8, C15orf48, PCOLCE2, CXCL10, GOLM1 and GPX2. The Venn diagram in Fig. 1indicates the comparison of common upregulated genes.

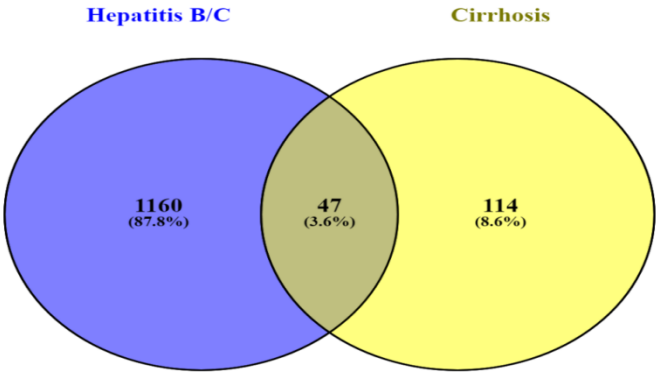
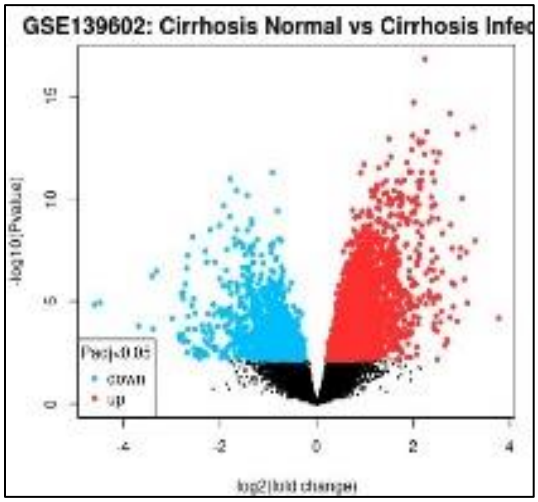


Figure 1: Elevated and differentially expressed genes often While 114 genes were discovered to be upregulated owing to cirrhosis and 1,160 genes were found to be upregulated due to hepatitis B/C infection, 47 genes were found to be elevated regardless of the cause.



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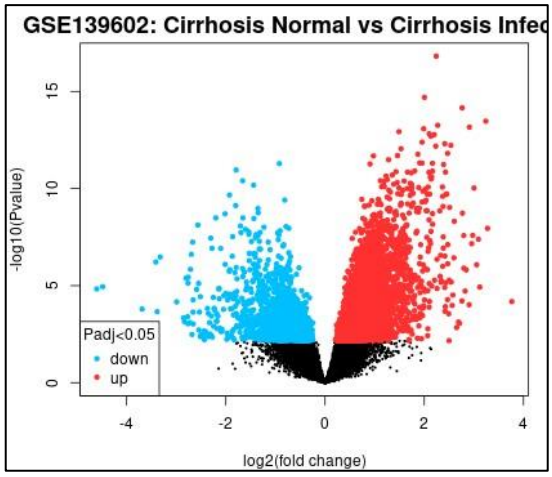

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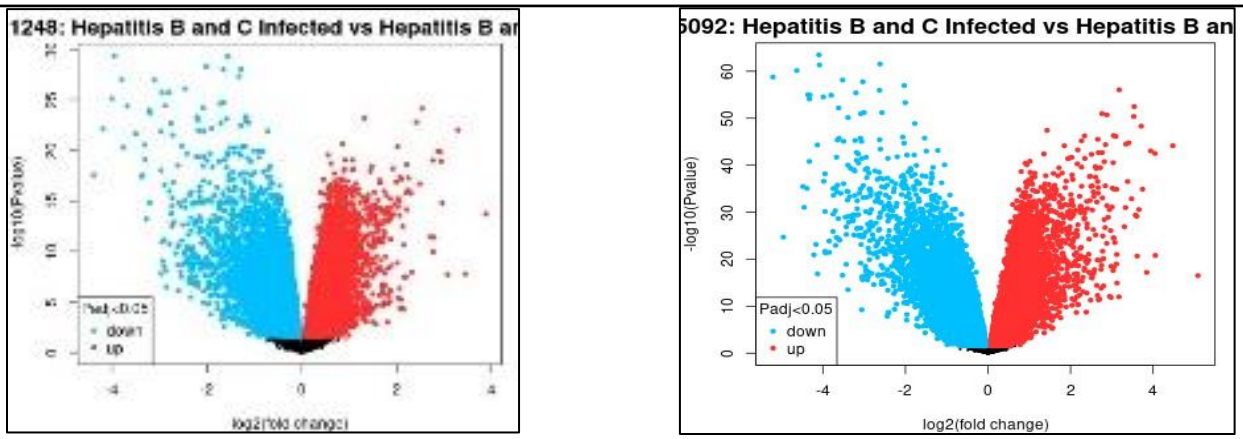

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Figure 2. 3D volcano graphs illustrating the location of 221 differentially expressed genes (DEGs) in hepatitis B/C in GSE121248 and GSE55092 and in 222 cirrhosis in GSE89377 and GSE139602. The green dots represent 223 upregulated genes, the red dots 223 downregulated genes and the black dots genes that remained unchanged.

3.2. Enrichment analysis of common upregulated genes

In order to evaluate the improved genes, the Enrichr platform was used to examine their GO and associated pathways. Table 1 lists the ontologies from the three GO subsections 227 (cellular component, molecular function and biological process) that were determined to be significant ($p < 0.05$). The table lists 228 biological processes, including the cellular response to shear stress in laminar flows and the management of natural killer cells. Additional molecular functions, including those of beta-galactoside (CMP) alpha-2,3-sialyltransferases and transmembrane transporters, were also uncovered. The zonula adherens and the t-cell receptor complex were also considered potential biological components.

ID	Description	pvalue	genes	Count
hsa04114	Oocyte meiosis	0.000510486	CCNB2/CDC20/PTTG1/AURKA	4
hsa04512	ECM-receptor interaction	0.002037412	SPP1/COL1A2/COL4A1	3
hsa00790	Folate biosynthesis	0.002542327	AKR1B10/AKR1C3	2
hsa04110	Cell cycle	0.005745129	CCNB2/CDC20/PTTG1	3
hsa03320	PPAR signaling pathway	0.019900349	ACSL4/FABP4	2
hsa04510	Focal adhesion	0.020481174	SPP1/COL1A2/COL4A1	3
hsa05166	Human T-cell leukemia virus 1 infection	0.02586964	CCNB2/CDC20/PTTG1	3
hsa00130	Ubiquinone and other terpenoid-quinone biosynthesis	0.031659609	NQO1	1
hsa04933	AGE-RAGE signaling pathway in diabetic complications	0.033966036	COL1A2/COL4A1	2
hsa04914	Progesterone-mediated oocyte maturation	0.035220997	CCNB2/AURKA	2
hsa05146	Amoebiasis	0.035220997	COL1A2/COL4A1	2

hsa04974	Protein digestion and absorption	0.035855261	COL1A2/COL4A1	2
hsa04620	Toll-like receptor signaling pathway	0.036494008	SPP1/CXCL10	2
hsa00061	Fatty acid biosynthesis	0.051304057	ACSL4	1
hsa04926	Relaxin signaling pathway	0.053836402	COL1A2/COL4A1	2
hsa00670	One carbon pool by folate	0.056846235	TYMS	1
hsa04120	Ubiquitin mediated proteolysis	0.063810789	CDC20/UBE2C	2
hsa05165	Human papillomavirus infection	0.070062641	SPP1/COL1A2/COL4A1	3
hsa04151	PI3K-Akt signaling pathway	0.082115791	SPP1/COL1A2/COL4A1	3
hsa01523	Antifolate resistance	0.084094909	TYMS	1
hsa00052	Galactose metabolism	0.086777897	AKR1B10	1
hsa00051	Fructose and mannose metabolism	0.092121296	AKR1B10	1
hsa00040	Pentose and glucuronate interconversions	0.097434724	AKR1B10	1
hsa04216	Ferroptosis	0.113196796	ACSL4	1
hsa00071	Fatty acid degradation	0.118391946	ACSL4	1
hsa05205	Proteoglycans in cancer	0.119436238	GPC3/COL1A2	2
hsa04913	Ovarian steroidogenesis	0.138882373	AKR1C3	1
hsa04979	Cholesterol metabolism	0.138882373	SORT1	1
hsa00480	Glutathione metabolism	0.153949855	GPX2	1
hsa01212	Fatty acid metabolism	0.153949855	ACSL4	1
hsa00240	Pyrimidine metabolism	0.156436409	TYMS	1
hsa04923	Regulation of lipolysis in adipocytes	0.156436409	FABP4	1
hsa00590	Arachidonic acid metabolism	0.163854122	AKR1C3	1
hsa00140	Steroid hormone biosynthesis	0.166312772	AKR1C3	1
hsa00561	Glycerolipid metabolism	0.166312772	AKR1B10	1
hsa04929	GnRH secretion	0.171209303	SPP1	1
hsa04920	Adipocytokine signaling pathway	0.183330348	ACSL4	1
hsa04622	RIG-I-like receptor signaling pathway	0.188131041	CXCL10	1
hsa01524	Platinum drug resistance	0.192904683	TOP2A	1
hsa04115	p53 signaling pathway	0.192904683	CCNB2	1
hsa04623	Cytosolic DNA-sensing pathway	0.197651419	CXCL10	1
hsa04918	Thyroid hormone synthesis	0.197651419	GPX2	1
hsa04146	Peroxisome	0.214055207	ACSL4	1
hsa01232	Nucleotide metabolism	0.220986576	TYMS	1
hsa04976	Bile secretion	0.230137323	SLC51B	1
hsa05222	Small cell lung cancer	0.236932688	COL4A1	1
hsa04657	IL-17 signaling pathway	0.241430956	CXCL10	1
hsa04640	Hematopoietic cell lineage	0.252565722	CD24	1
hsa04061	Viral protein interaction with cytokine and cytokine receptor	0.254773799	CXCL10	1
hsa04668	TNF signaling pathway	0.285038062	CXCL10	1
hsa04670	Leukocyte transendothelial migration	0.285038062	THY1	1
hsa04722	Neurotrophin signaling pathway	0.295558471	SORT1	1
hsa04611	Platelet activation	0.305930436	COL1A2	1

hsa04068	FoxO signaling pathway	0.32020561	CCNB2	1
hsa04142	Lysosome	0.322221807	SORT1	1
hsa04371	Apelin signaling pathway	0.336175577	SPP1	1
hsa05418	Fluid shear stress and atherosclerosis	0.336175577	NQO1	1
hsa01240	Biosynthesis of cofactors	0.363261704	NQO1	1
hsa04218	Cellular senescence	0.368926462	CCNB2	1
hsa05160	Hepatitis C	0.370803959	CXCL10	1
hsa05225	Hepatocellular carcinoma	0.391106275	NQO1	1
hsa05164	Influenza A	0.396533372	CXCL10	1
hsa04062	Chemokine signaling pathway	0.433245615	CXCL10	1
hsa05169	Epstein-Barr virus infection	0.4499659	CXCL10	1
hsa05415	Diabetic cardiomyopathy	0.451611682	COL1A2	1
hsa05203	Viral carcinogenesis	0.453252744	CDC20	1
hsa05170	Human immunodeficiency virus 1 infection	0.466212876	CCNB2	1
hsa04714	Thermogenesis	0.497337895	ACSL4	1
hsa05171	Coronavirus disease - COVID-19	0.497337895	CXCL10	1
hsa05132	Salmonella infection	0.522419573	S100A10	1
hsa04060	Cytokine-cytokine receptor interaction	0.584417767	CXCL10	1
hsa05016	Huntington disease	0.598057429	GPX2	1
hsa05206	MicroRNAs in cancer	0.602910104	CDCA5	1
hsa05014	Amyotrophic lateral sclerosis	0.66316943	GPX2	1
hsa05022	Pathways of neurodegeneration - multiple diseases	0.76144915	GPX2	1

3.3. Network analysis

We obtained the matched network using Cytoscape's STRING protein quarry plugin function. Finding hub genes and then suggesting common pharmaceutical molecules for cirrhosis and hepatitis B/C were the goals of storing this network. Finding shared genetic factors between cirrhosis and hepatitis B/C and developing effective treatments for both diseases were the primary aims of this study. The network has 55 nodes and 93 edges, as shown in Figure 3.

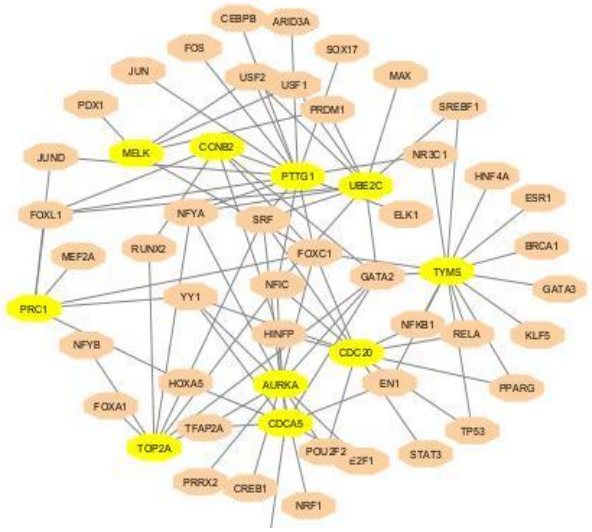

Figure 3. A complex network of genetic and protein-protein interactions (PPIs) connects cystic fibrosis to hepatitis B/C. Genes that are often upregulated are shown by the light orange nodes. The 55 nodes and 93 edges make up this network.

3.4. Hub genes identification and module analysis

Genes in the PPIs network are highly connected to one another and CytoHubba was used to separate them. The degree method was used to identify the hub genes. The 10 genes—CDC20, CCNB2, MELK, AURKA, PRC1, TOP2A, CDCA5, PTTG1, TYMS and UBE2C—were shown to function as hub genes (Fig. 4). An region with a high concentration of PPIs networks was, however, located using MCODE. As seen in Figure 4, this clustering network yielded two hub genes, TOP2A and UBE2C.

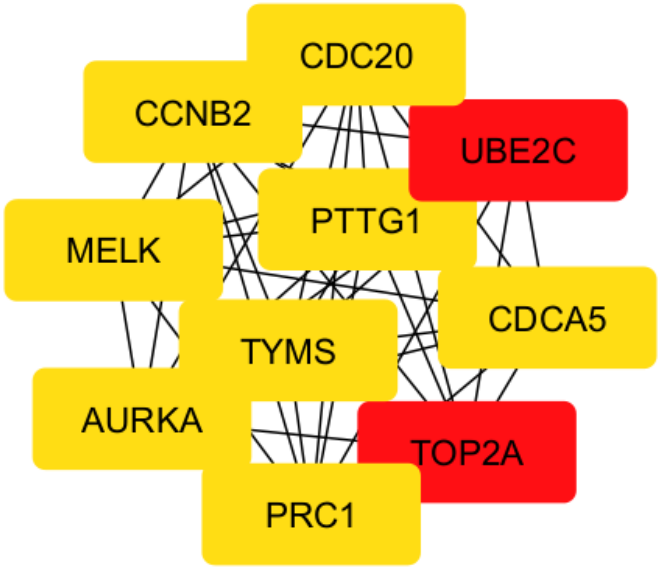

Figure 4. An analysis network built using principal component analyses (PPIs). This diagram depicts the PPIs network as a highly interconnected web. Through clustering, eleven hub genes were able to produce TOP2A and UBE. The two hub genes are shown by the red light.

3.5. Transcriptional factor regulatory network of hub genes

A transcription factor regulatory network for hub genes was constructed using the NetworkAnalyst platform. Eleven transcription factors and twenty-seven interactions make up this network. A total of twelve transcription factors were found to regulate UBE2C: two as TOP2A, four as CDC20, nine as TYMS, three as PTTG1, two as CCNB2 and one as PRC1. There were eight TFs in the TF regulatory network that had a degree of connection of 2 or higher.

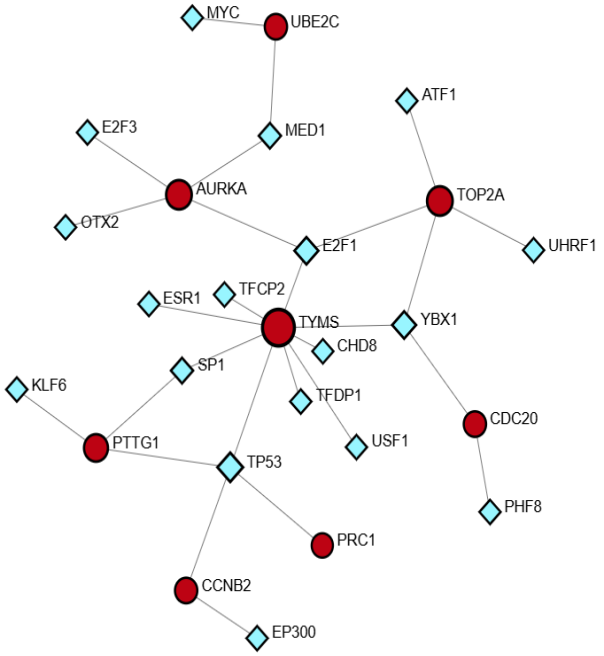

Figure 5. Structure of the link between hub genes and transcription factors. Each node represents a different TF gene; the red one represents the hub gene. Eight transcription factors and eight hub genes make it up.

3.6. TFs-miRNA regulatory network analysis

The TFs-miRNA regulatory Network explains the complex interplay between TFs, miRNAs and hub genes. A TF-miRNA coregulatory network with 105 nodes and 132 edges was investigated using NetworkAnalyst.

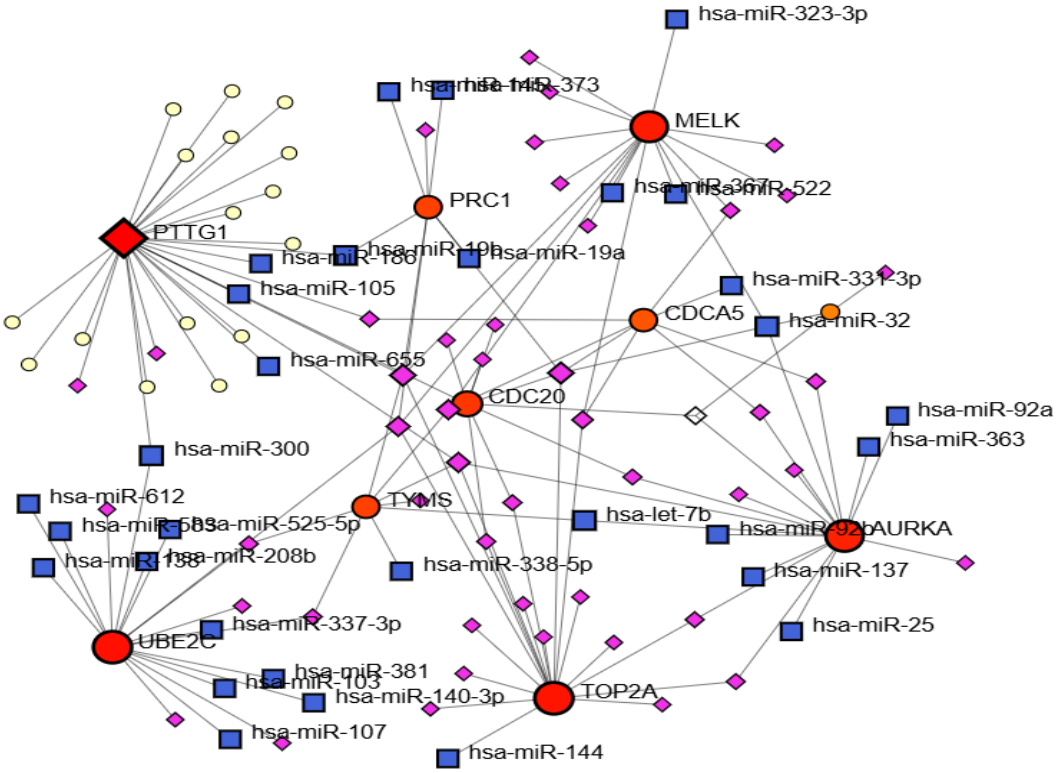

Figure 6. The model shows how TF-miRNA regulates a network of shared hub genes.

3.7. Protein drug interaction network

The key to successful patient treatment is a thorough understanding of protein drug interaction networks. Retrieved from DrugBank, this protein drug interaction network primarily associates VDR with 33 different pharmaceutical classes. Cirrhosis and hepatitis B/C regulation may be significantly aided by vitamin D and related compounds, according to this network. In Figure 7, we can see the medication network.

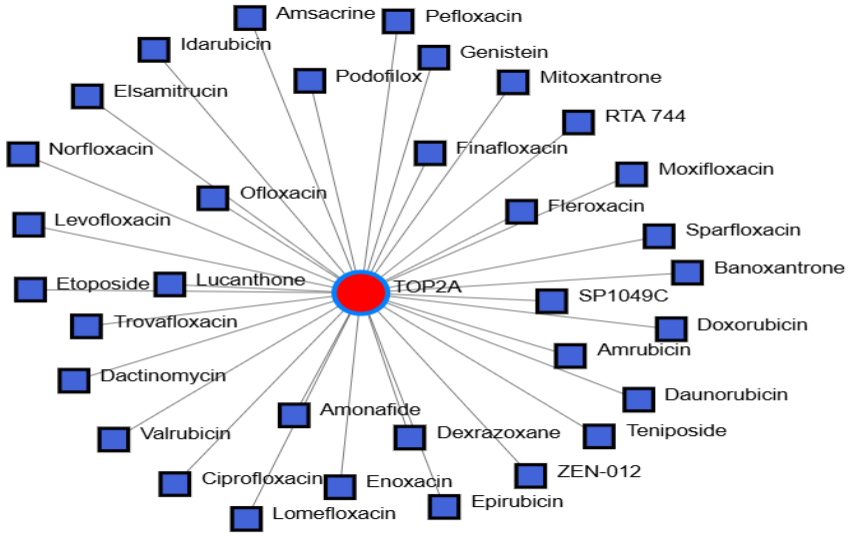

Figure 7. Drugs protein interaction network.

Discussion

This study highlights the shared genetic aspects of Hepatitis B and C infections and their progression to cirrhosis. By employing a network-based approach and analyzing gene expression data from various datasets, we identified 47 common upregulated genes, with ten key hub genes in which only one gene TOP2A emerged as critical player in disease progression. The findings emphasize the importance of a systems biology perspective, which enables a holistic understanding of the interactions among genes and pathways. These insights not only enhance our knowledge of the molecular underpinnings of hepatitis-related liver disease but also open avenues for future research focused on therapeutic interventions. Targeting the identified hub genes may offer promising strategies for mitigating the progression of liver disease in patients with chronic HBV and HCV infections. This research underscores the need for continued exploration of the genetic and molecular factors contributing to liver disease, aiming to improve patient outcomes and public health in the face of ongoing global challenges posed by viral hepatitis, though it is limited by reliance on in silico data without experimental validation, potential biases from combining datasets from different platforms and a lack of longitudinal data to confirm causality between gene expression and cirrhosis progression. Further studies are essential to validate these findings, particularly by investigating the role of specific genes in liver fibrosis models, which could elucidate their mechanisms and contributions to disease progression, ultimately translating these insights into effective clinical applications.

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