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Decoding Genetic Risk: A Genome-Wide Association and Functional Analysis of Variants Linked to Liver Cancer Susceptibility

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ABSTRACT: Liver cancer is one of the leading causes of cancer death worldwide. Genetic factors play a role in determining a person's susceptibility to this disease. Genome-Wide Association Studies (GWAS) have identified several genetic variants associated with liver cancer, but their functional mechanisms still need to be further explored. Therefore, this study aims to identify genetic variants that contribute to liver cancer, evaluate their functional effects on proteins, analyze allele frequencies across global populations, and examine gene expression in various human tissues. This study used a bioinformatics approach to identify genetic variations associated with liver cancer from the GWAS Catalog. Five selected missense variants were analyzed using SIFT and PolyPhen-2 to assess their functional impact. Allele distributions in the global population were analyzed using 1000 Genomes Project data, and gene expression was analyzed using the GTEx Portal. The analysis identified 77 candidate genes with significant associations with liver cancer, based on p-values meeting the threshold ($p < 5 \times 10^{-8}$). Five genes in the *Missense Variant category* showed a strong association with liver cancer: *IFNL3, SLC30A10, PNPLA3, OSMR,* and *CMTR2.* In the analysis using SIFT and PolyPhen-2, the rs3096380 variant (*CMTR2*) was *deleterious, and* rs738409 (*PNPLA3*) and rs188273166 (SLC30A10) were *deleterious* and *probably damaging,* with the potential to disrupt protein function and contribute to the pathogenesis of liver cancer. Conclusion: Genetic variations rs738409 (*PNPLA3*) and rs188273166 (SLC30A10) are *deleterious* and *probably damaging*, potentially disrupting protein function and contributing to liver cancer pathogenesis.

Keywords: Liver cancer, GWAS, *PNPLA3*, SLC30A10, rs738409, rs188273166.

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INTRODUCTION

Liver cancer is one of the leading causes of cancer death worldwide, with the incidence rate continuing to increase every year (Cao et al., 2021). Based on data from the *Global Cancer Observatory* (GLOBOCAN), liver cancer is ranked sixth as the most common cancer and the third highest cause of death from cancer globally (Cao et al., 2024). This high mortality rate is caused by various factors, including late diagnosis, limited therapeutic options, and the complexity of the molecular mechanisms underlying the development of the disease (Guo et al., 2024). Liver cancer can be triggered by various risk factors, such as hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, chronic alcohol consumption, obesity, non-alcoholic fatty liver disease (NAFLD), and exposure to carcinogenic substances such as aflatoxin (Ashtari et al., 2015). In addition to environmental factors, genetic predisposition also plays a role in determining a person's susceptibility to liver cancer, which is still a rapidly developing area of research (McGlynn et al., 2021).

In general, liver cancer is divided into several types based on cellular origin. Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, accounting for about 75–85% of all cases (Miao et al., 2022). In addition, there is cholangiocarcinoma (CCA) originating from the intrahepatic bile duct, as well as angiosarcoma and hepatoblastoma, which are less common. In addition to primary liver cancer, the liver is also an organ that often experiences metastasis from cancers in other organs, such as colorectal, breast, and lung cancers, known as secondary liver cancer (Hewitt et al., 2022). These differences in cancer types indicate that liver cancer is not a single entity, but rather a group of diseases with diverse etiologies and pathogenesis (Yang et al., 2021).

A thorough understanding of the genetic factors underlying liver cancer is essential to improve prevention strategies, early detection, and precision-based treatment. Genome-wide association studies (GWAS) have become an important tool for identifying genetic variants associated with liver cancer risk (Amukti et al., 2024). Several GWAS studies have identified single-nucleotide polymorphisms (SNPs) that may contribute to liver cancer pathogenesis through mechanisms involving immune regulation, lipid metabolism, and inflammatory pathways (Gumelar et al., 2024). However, most of these results still require further validation and in-depth exploration of how these genetic variations affect disease risk across different populations. Therefore, a combination of genomic approaches, functional analysis, and population-based studies is needed to understand the role of genetic variations in liver cancer susceptibility (Zhang et al., 2016).

This study aims to integrate GWAS results with functional analysis to explore the role of genetic variations in liver cancer (Chatziparasidou et al., 2024). Using bioinformatics approaches and large-scale genomic data, this study will identify genetic variants associated with liver cancer, evaluate their impact on gene regulation and metabolic pathways, and analyze allele frequency distributions across populations (Humolungo et al., 2024). The results of this study are expected to provide new insights into the genetic mechanisms underlying liver cancer, as well as to open opportunities for the development of more effective gene-based diagnostic biomarkers and therapies for its management.

METHODS

Study design

This study employed a bioinformatics approach to identify and analyze genetic variations associated with liver cancer susceptibility (Amukti et al., 2024). The research

workflow included identifying genetic variants in the GWAS Catalog, predicting their functional impact, analyzing allele distributions across global populations, and analyzing gene expression using public databases (Gumelar et al., 2024).

Ethical statement

This study employed a bioinformatics approach to identify and analyze genetic variations associated with liver cancer susceptibility. All data used in this research were obtained from publicly available databases, including the GWAS Catalog and gene expression repositories. No human subjects, animal models, or personally identifiable information were involved in this study. Therefore, ethical approval was not required. The study complies with ethical guidelines for the use of open-access genomic data (Manduchi et al., 2019).

Materials

The study utilized publicly available genomic and transcriptomic databases, including the GWAS Catalog (https://www.ebi.ac.uk/gwas/) for identifying genetic variants associated with liver cancer (Linskey et al., 2021). SNPnexus (https://www.snp-nexus.org/) for functional impact analysis of genetic variations. 1000 Genomes Project data available on SNPnexus for allele distribution analysis across global populations. GTEx Portal (https://gtexportal.org/) for gene expression analysis in liver tissue(Gumelar et al., 2024).

Procedures

Identification of Genetic Variations through GWAS Catalog

A systematic search was performed in the GWAS Catalog using the keyword "Liver Cancer" to identify genetic variations significantly associated with liver cancer ($p < 5 \times 10^{-8}$). The search yielded 77 candidate genes harbouring missense variants associated with liver cancer susceptibility. These genes were further analyzed to identify specific variations contributing to disease susceptibility (Amukti et al., 2024).

Prediction of Functional Impact of Genetic Variations

The genetic variants identified in the GWAS Catalog were further analyzed using SNPnexus to assess their functional impact. The analysis included: Sorting Intolerant from Tolerant (SIFT) to determine whether the missense mutations were likely pathogenic. Variants categorized as deleterious were prioritized for further investigation. Polymorphism Phenotyping v2 (PolyPhen-2) to predict structural or functional changes in proteins due to missense mutations. Variants were classified as benign, possibly damaging, or probably damaging (Gumelar et al., 2024).

Allele Distribution Analysis in Global Populations

The allele frequencies of the identified genetic variants were analyzed using the 1000 Genomes Project dataset available on SNPnexus. The analysis evaluated allele distribution across different populations, including African (AFR), American (AMR), European (EUR), East Asian (EAS), and South Asian (SAS). This step aimed to uncover potential genetic predisposition differences among ethnic groups (Bharti et al., 2024).

Gene Expression Analysis Related to Liver Cancer

The GTEx Portal was used to investigate the expression levels of genes containing significant genetic variations in liver tissue. This analysis compared gene expression between individuals carrying risk alleles and those without risk alleles. Additionally, the relationship between these gene expressions and liver cancer-related metabolic pathways was examined (Amukti et al., 2024).

Statistical Analysis

Descriptive statistics were used to summarize allele frequencies across different populations. Functional prediction results from SIFT and PolyPhen-2 were categorized and analyzed to determine their pathogenic significance. Sorting Intolerant From Tolerant (SIFT) to determine whether the missense mutations were. likely pathogenic Variants categorized as deleterious (SIFT score ≤ 0.05) were prioritized for further investigation. Polymorphism Phenotyping v2 (PolyPhen-2) to predict structural or functional changes in proteins due to missense mutations. Variants were classified as benign (score 0.0–0.449), possibly damaging (score 0.450–0.849), or probably damaging (score ≥ 0.85) (Gumelar et al., 2024).

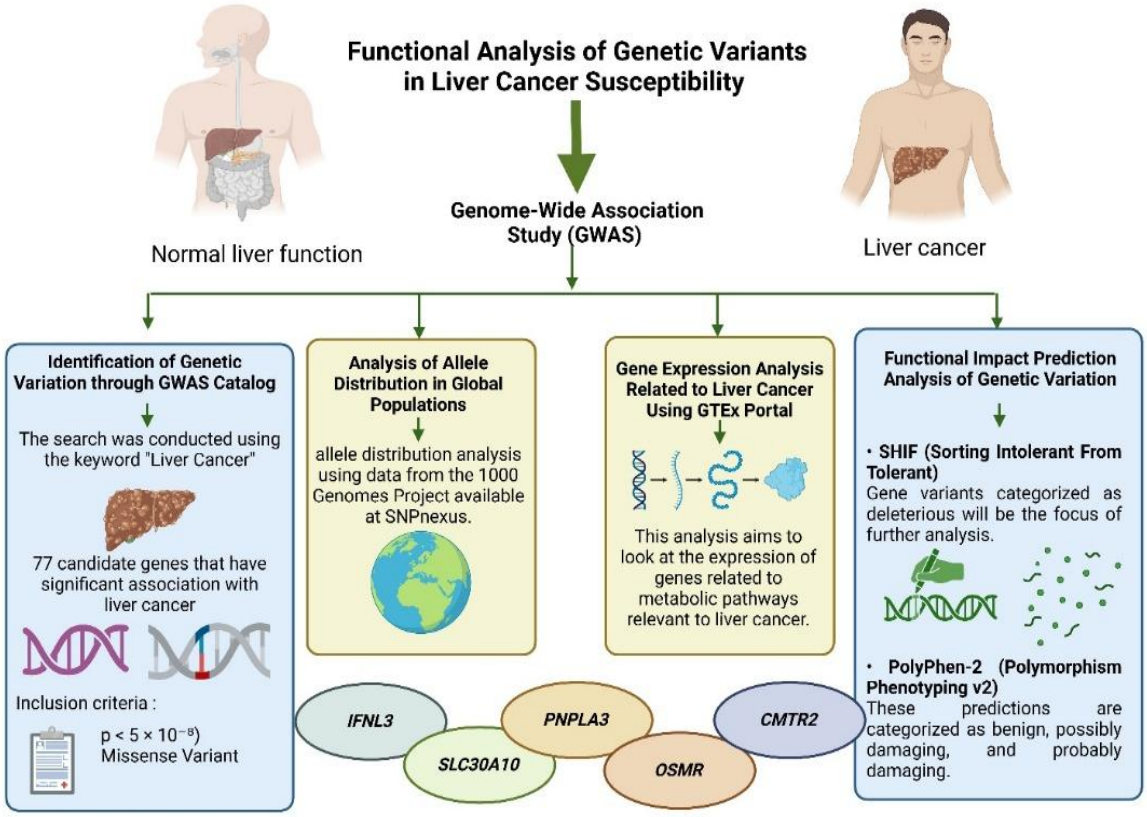

Figure 1. Research methods flowchart. Created at https://BioRender.com

RESULT AND DISCUSSION

Identification of Genetic Variation through GWAS Catalog

This study successfully identified genetic variants potentially associated with liver cancer susceptibility using a bioinformatics approach (Pratiwi et al., 2024). From the GWAS Catalog search results, 77 candidate genes were identified that showed significant association with liver cancer, with *p-values* below the threshold ($p < 5 \times 10^{-8}$). However, for further analysis, five genes in the *Missense Variant category* were selected for their strong association with liver cancer: *IFNL3, SLC30A10, PNPLA3, OSMR,* and *CMTR2.* Each identified gene harbours a genetic variant (a single-nucleotide *polymorphism*) that plays a

role in the molecular mechanism of liver cancer. As shown in Table 1, genetic variants with high significance levels include rs738409 in *PNPLA3* (*p* = 5.00E-40), rs34675408 in *OSMR* (*p* = 1.00E-32), and rs8103142 in *IFNL3* (*p = 6.00E-12). All three variants are missense* mutations, which have the potential to cause changes in protein function and contribute to liver cancer pathogenesis (Togninalli et al., 2018).

Table 1. Missense Variant Data and p-value 10^{-8} Gene Categories that have the potential to cause liver cancer.

Gene	Gene Variants	Variant Mutation	P Value
IFNL3	rs8103142	*missense_variant*	6.00E-12
SLC30A10	rs188273166	*missense_variant*	1.00E-08
PNPLA3	rs738409	*missense_variant*	5.00E-40
OSMR	rs34675408	*missense_variant*	1.00E-32
CMTR2	rs3096380	*missense_variant*	1.00E-17

Analysis of Prediction of Functional Impact of Genetic Variation

To evaluate the functional impact of the genetic variations identified in this study, an analysis was performed using SNPnexus, with the SIFT (Sorting Intolerant From Tolerant) and PolyPhen-2 (Polymorphism Phenotyping v2) approaches (Gumelar et al., 2024). This analysis aims to predict whether *missense mutations* in genetic variants can cause significant changes in protein function, potentially affecting the development of liver cancer. The results of the analysis using SIFT (Table 2) showed that three variants, namely rs188273166 (SLC30A10), rs3096380 (*CMTR2*), and rs738409 (*PNPLA3*), were categorized as deleterious, with a score of ≤ 0.05, indicating that the amino acid changes caused by these mutations can disrupt protein function. Meanwhile, the other two variants, rs8103142 (*IFNL3*) and rs34675408 (*OSMR*), were categorized as tolerated, indicating that these mutations are unlikely to hurt protein function.

Table 2. Prediction of the impact of genetic variants on proteins using the SIFT method

Variant Gene	Chromosome	Variants	Transcript	AA Position	Wild AA	Mutant AA	Score	Prediction
rs188273166	chr1	G/A	ENST00000356609	95	T	I	0.000	*Deleterious*
rs3096380	chr16	G/C	ENST00000567610	60	L	V	0.050	*Deleterious*
rs738409	chr22	C/G	ENST00000216180	148	I	M	0.000	*Deleterious*
rs8103142	chr19	T/C	ENST00000413851	70	K	R	0.451	*Tolerated*
rs34675408	chr5	T/G	ENST00000274276	187	H	Q	0.298	*Tolerated*

Further analysis using PolyPhen-2 (Table 3) showed that two variants, rs738409 (*PNPLA3*) and rs188273166 (SLC30A10), were categorized as probably damaging, with scores of 0.655 and 0.686, respectively, indicating that these mutations are likely to cause structural and functional changes in the protein. In contrast, the variants rs3096380, rs8103142, and rs34675408 were categorized as benign, meaning that these mutations are unlikely to have a significant impact on protein function.

Table 3. Prediction of the impact of genetic variants on proteins using the polyphen method

Variant Gene	Chromosome	Variants	Transcript	AA Position	Wild AA	Mutant AA	Score	Prediction
rs738409	chr22	C/G	ENST00000216180	148	I	M	0.655	*Probably Damaging*
rs188273166	chr1	G/A	ENST00000356609	95	T	I	0.686	*Probably Damaging*
rs3096380	chr16	G/C	ENST00000568910	60	L	V	0.010	*Benign*
rs8103142	chr19	T/C	ENST00000413851	70	K	R	0.003	*Benign*
rs34675408	chr5	T/G	ENST00000274276	187	H	Q	0.001	*Benign*

Analysis of Allele Distribution in Global Populations

Allele distribution analysis across global populations was performed to evaluate variation in the minor allele frequency (MAF) of the five genetic variants identified in this study (Ohi et al., 2017). Data were obtained from a global population genetic database, covering African (AFR), American (AMR), East Asian (EAS), European (EUR), and South Asian (SAS) populations (Fan et al., 2023). The analysis results (Table 4) showed that the distribution of minor alleles varied significantly across populations. For example, the rs188273166 (SLC30A10) variant had a very low minor allele frequency and was detected in only small numbers in the AMR (0.0029) and EUR (0.0030) populations, but was not detected in the other populations. This suggests that this mutation may be less common in the global population. In contrast, the rs3096380 (*CMTR2*) variant showed a high prevalence in all populations, with a minor allele frequency of more than 80% in all ethnic groups analyzed. The SAS and EUR populations had the highest frequencies, 0.9673 and 0.9652, respectively, while the EAS population had a slightly lower frequency (0.8284). The rs8103142 (*IFNL3*) variant, which has been associated with a variety of inflammatory and immunological conditions, had the highest minor allele frequency in the African population (0.6952) and lower frequencies in the European (0.3121) and South Asian (0.2372) populations. Interestingly, this variant had an exceptionally low frequency in the East Asian population (0.0833), suggesting possible differences in genetic adaptation between populations. For the rs738409 (*PNPLA3*) variant, previously categorized as *probably damaging* in the PolyPhen-2 analysis, the minor allele frequency was quite high in the American (0.4841) and East Asian (0.3502) populations, but lower in the African (0.1180) population. This is in line with previous studies showing that *PNPLA3* variants are frequently associated with non-alcoholic fatty liver disease (NAFLD) in certain populations. Finally, the rs34675408 (*OSMR*) variant has the highest minor allele frequency in African populations (0.1513), whereas in other populations it is relatively low, especially in East Asia (0.0268) and America (0.0634).

Table 4. Distribution of Alleles in Global Populations

Variant Gene	REF Allele	ALT Allele	Minor Allele	AFR Frequency	AMR Frequency	EAS Frequency	EUR Frequency	SAS Frequency
rs188273166	G	A	A	0	0.002900	0	0.003000	0
rs3096380	G	A	G	0.954600	0.900600	0.828400	0.965200	0.967300
rs8103142	T	C	C	0.695200	0.404900	0.083300	0.312100	0.237200
rs738409	C	G	G	0.118000	0.484100	0.350200	0.225600	0.246400
rs34675408	T	G	G	0.151300	0.063400	0.026800	0.084500	0.143100

Gene Expression Analysis Related to Liver Cancer Using GTEx Portal

Analysis of *IFNL3* gene expression using data from the GTEx Portal showed the highest expression in testicular tissue, not in the liver (Figure 2). This indicates that *IFNL3* may play a role in the regulation of testicular functions, such as spermatogenesis or immunological processes related to the male reproductive system(Amanzada et al., 2015). Although the liver is a major organ involved in metabolism and detoxification, the lower expression of *IFNL3* in the liver compared to the testis suggests that its role in liver cancer may be more of a systemic regulator than a direct expression factor in liver tissue. However, the expression that is still detected in the liver may still have an impact on inflammation and immune responses that contribute to the pathogenesis of liver cancer. These findings suggest that although *IFNL3* may not be a gene highly expressed in the liver, it may play a role in liver cancer through paracrine or systemic mechanisms, such as interactions with the immune system or responses to viral infections. Further studies are needed to understand how *IFNL3* expression in the testis relates to the mechanism of liver cancer and whether there is a cross-regulatory pathway between these two organs.

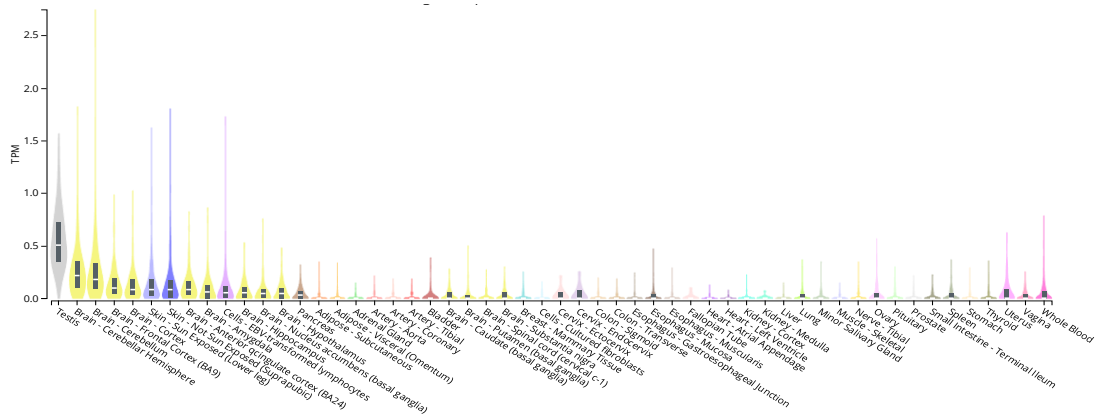

Figure 2. Gene expression of *IFNL3* in human body tissue

Analysis of *SLC30A10* gene expression using data from the GTEx Portal showed that the highest expression occurred in the liver, as shown in Figure 3. The *SLC30A10* gene

encodes a zinc transporter *that* plays a role in mineral homeostasis, especially in manganese and zinc metabolism(Mercadante et al., 2019). High expression in the liver suggests that *SLC30A10* plays an important role in the detoxification and excretion of heavy metals, as well as in maintaining the balance of minerals required for normal cellular function. These results are also in line with previous studies that have linked mutations in *SLC30A10* to impaired manganese metabolism, which can lead to liver damage and neurological disorders. In the context of liver cancer, high expression of *SLC30A10* in the liver may indicate its involvement in cellular defense mechanisms against oxidative stress and heavy metal toxicity, which may affect the development or progression of liver cancer.

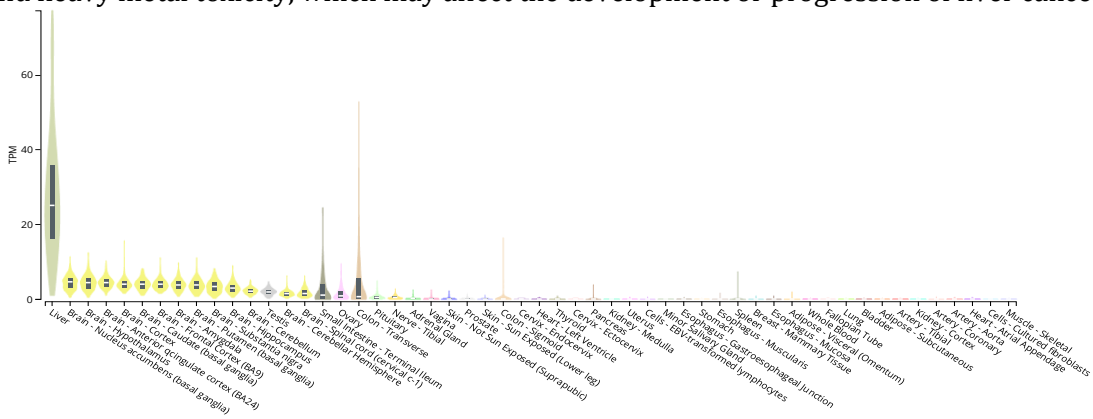

Figure 3. Gene expression of *SLC30A10* in human body tissues

Analysis of *the PNPLA3* gene expression in the GTEx Portal showed the highest expression in the liver (Figure 4). The *PNPLA3* gene (*patatin-like phospholipase domain-containing protein 3*) plays an important role in lipid metabolism and triglyceride storage in hepatocytes(Liu & Park, 2024). High expression of *PNPLA3* in the liver suggests that this gene is directly involved in regulating lipid homeostasis, with important implications for the development of liver diseases, including non-alcoholic hepatic steatosis (NAFLD) and liver cancer (HCC). Previous studies have shown that the rs738409 (I148M) variant in *PNPLA3* is strongly associated with increased liver fat accumulation, which may increase the risk of liver fibrosis and hepatocarcinogenesis. These findings further strengthen that *PNPLA3* is a major genetic factor in the development of liver disease, especially in individuals with certain genetic predispositions. Overall, high PNPLA3 expression in the liver suggests that this gene plays an important role in the pathophysiology of liver cancer, particularly through dysregulation of lipid metabolism. Therefore, *PNPLA3* may be a potential target for liver cancer therapy research and a biomarker for evaluating chronic liver disease risk (Rady et al., 2021).

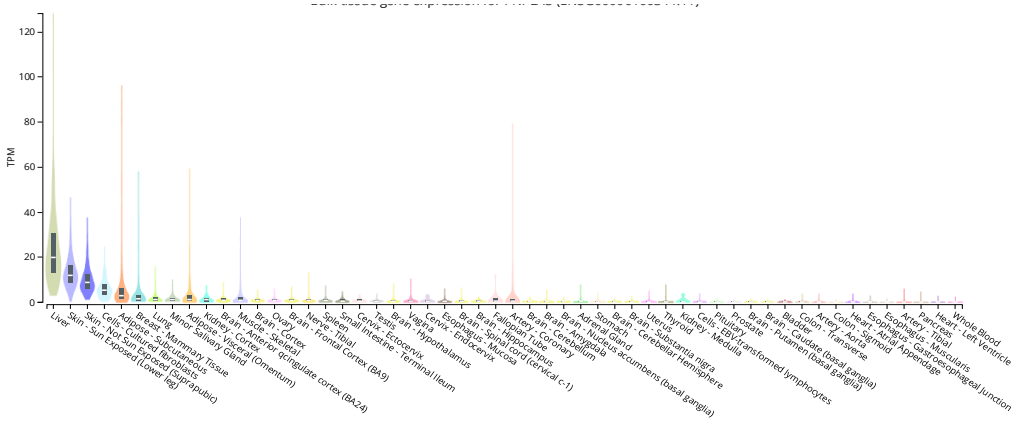

Figure 4. Gene expression of *PNPLA3* in human body tissues

Analysis of *OSMR* gene expression using data from the GTEx Portal revealed the highest expression in fibroblastic cell culture (Figure 5). The *OSMR* (Oncostatin M Receptor) gene is an important component of the IL-6 cytokine signalling pathway. It plays a major role in cell proliferation, differentiation, and the inflammatory response (Zhu et al., 2020). High expression of *OSMR* in fibroblasts suggests that this gene is likely involved in tissue remodelling, fibrosis, and wound healing, as well as in the dynamics of the tumor microenvironment. In the context of liver cancer (hepatocellular carcinoma, HCC), the role of *OSMR* is increasingly attracting attention, as several studies have linked its activation to increased cancer cell proliferation and resistance to apoptosis via the JAK/STAT and MAPK pathways. Although *OSMR* expression in the liver is relatively lower compared to fibroblasts, the role of fibroblasts in supporting tumor growth through cellular interactions and secretion of pro-tumorigenic factors cannot be ignored. These results indicate that *OSMR* may play a role in the liver tumor microenvironment, especially through the activation of fibroblasts that support cancer progression.

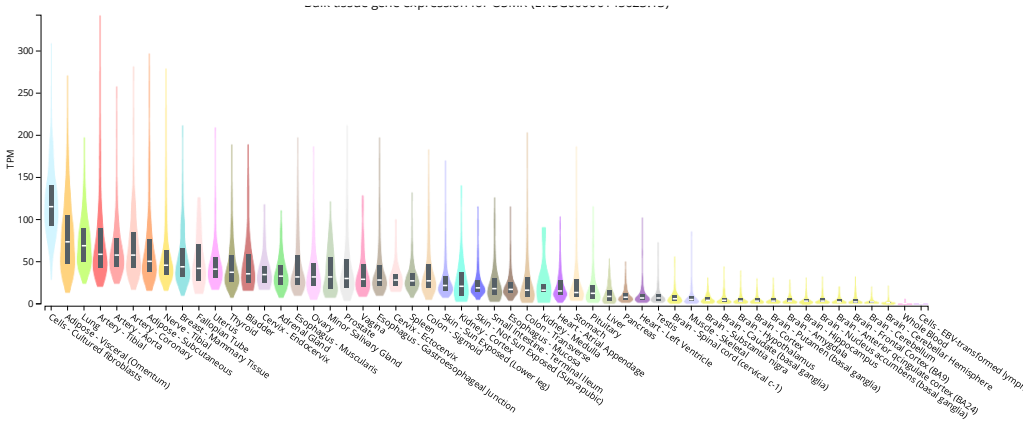

Figure 5. *OSMR* gene expression in human body tissues

Analysis of *the CMTR2* gene expression using data from the GTEx Portal showed the highest expression in EBV-transformed lymphocytes (Figure 6). The *CMTR2* (Cap Methyltransferase 2) gene encodes an enzyme that plays a role in RNA modification,

specifically the methylation of the 5' end of mRNA, which contributes to mRNA stability and gene expression regulation. High expression of *CMTR2* in EBV-transformed lymphocytes indicates that this gene plays an important role in the proliferation and differentiation of immune cells, especially during viral infection and Epstein-Barr Virus (EBV)- mediated lymphocyte transformation (Inesta-Vaquera & Cowling, 2017). In the context of liver cancer (hepatocellular carcinoma, HCC), the relationship between *CMTR2* and liver cancer still needs to be explored further. However, the fact that the highest expression was found in EBV-transformed lymphocytes may indicate that this gene plays a role in the immune response to infection, which may contribute to the development of chronic inflammation that underlies hepatocarcinogenesis (Ignatochkina et al., 2024).

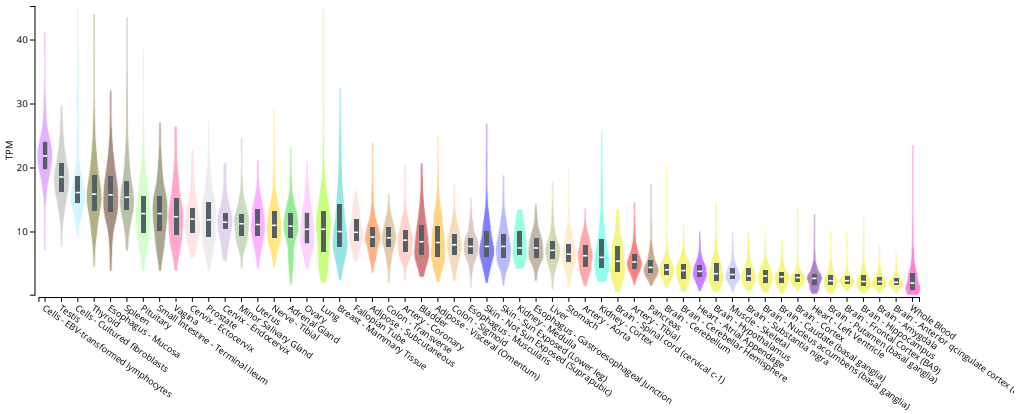

Figure 6. Gene expression of *CMTR2* in human body tissues.

The results of this study indicate that genetic variations identified through GWAS have great potential in understanding liver cancer susceptibility. The five missense variants analyzed showed varying degrees of functional impact on the encoded proteins. SIFT analysis indicated that the variants rs738409 (*PNPLA3*), rs188273166 (SLC30A10), and rs3096380 (*CMTR2*) were classified as *deleterious,* meaning they can cause structural changes that may damage protein function (Gumelar et al., 2024). Meanwhile, PolyPhen-2 results showed that the variants rs738409 (*PNPLA3*) and rs188273166 (SLC30A10) were classified as *probably damaging,* further supporting their role in liver cancer pathogenesis. The distribution of alleles across the global population also showed a varied pattern, suggesting the presence of population-specific genetic factors that may influence liver cancer risk. For example, the rs738409 variant in *PNPLA3* has a higher minor allele frequency in North American and East Asian populations, which may explain why individuals from these populations are at higher risk for non-alcoholic fatty liver disease (NAFLD), a major risk factor for the development of HCC. Similarly, the rs8103142 variant in *IFNL3*, which is associated with immune response and inflammation, has a higher frequency in African populations, suggesting that genetic and environmental factors may interact in determining liver cancer risk in certain populations(Amukti et al., 2024).

Gene expression analysis using the GTEx Portal revealed that the five genes analyzed showed distinct patterns across various human tissues. The highest expression of *IFNL3* was observed in the testis, indicating that although this gene is not predominantly

expressed in the liver, its role in immune regulation may influence liver cancer development through systemic or paracrine mechanisms. In contrast, the highest expression of *SLC30A10* and *PNPLA3* was observed in the liver, further confirming the direct roles of these two genes in mineral homeostasis and lipid metabolism, two factors that are highly influential in the pathogenesis of HCC (Zhang et al., 2016). Interestingly, *OSMR* showed the highest expression in cell culture fibroblasts, suggesting that this gene may play a greater role in the dynamics of the liver tumor microenvironment, particularly in supporting fibrosis and stromal cell activation. Activated fibroblasts in liver cancer are known to contribute to cancer cell proliferation, angiogenesis, and resistance to therapy. Meanwhile, the highest expression of *CMTR2* was observed in EBV-transformed lymphocytes, suggesting its involvement in the immune response and chronic inflammation, which may influence the development of HCC. Overall, the results of this study highlight the important role of the identified genetic variations in the mechanism of liver cancer, both directly through liver metabolism and inflammation, and indirectly through the immune system and tumor microenvironment (Byrne et al., 2015). These findings may form the basis for further research in the development of genetic biomarkers for early detection of liver cancer as well as potential targets for genetically-based therapies and immunotherapy.

CONCLUSION

The results of this study identified five missense variants, namely *IFNL3, SLC30A10, PNPLA3, OSMR,* and *CMTR2,* which have the potential to play a role in liver cancer. SIFT and PolyPhen-2 analysis showed that the genetic variants rs738409 (*PNPLA3*) and rs188273166 (SLC30A10) are *deleterious* and *probably damaging,* with the potential to disrupt protein function and contribute to the pathogenesis of liver cancer.

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AUTHOR CONTRIBUTION

DPA : study design, supervised the research process, and led the manuscript writing
DE : data acquisition, literature review, and manuscript drafting
TH : bioinformatics analysis and data interpretation
LA : bioinformatics analysis and data interpretation
IAS : conducted functional enrichment and assisted in figure preparation
MSB : result validation and critical manuscript revision
RIP : result validation and critical manuscript revision
IA : statistical analysis and supported data visualization
MM : manuscript review and final edit

ETHICS APPROVAL

This study did not involve any experiments on human participants or animals. All data analyzed in this research were obtained from publicly available databases. Therefore, ethical clearance was not applicable for this study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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