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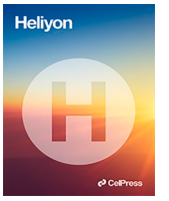

Research article

Computational network analysis of two popular skin cancers provides insights into the molecular mechanisms and reveals common therapeutic targets

Md Sujan Mahmud [a], Bikash Kumar Paul [b,d], Md. Rakibul Hasan [a], K.M. Tanjida Islam [c], Imran Mahmud [a], Shahin Mahmud [c,*]

[a] Department of Software Engineering, Daffodil International University, Bangladesh
[b] Department of Information and Communication Technology, Mawlana Bhashani Science and Technology University, Santosh, Tangail-1902, Bangladesh
[c] Department of Biotechnology and Genetic Engineering, Mawlana Bhashani Science and Technology University, Santosh, Tangail-1902, Bangladesh
[d] Department of Computing and Information System (CIS), Daffodil International University, Dhaka, Bangladesh

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ABSTRACT

Basal Cell Carcinoma (BCC) and Actinic Keratosis (AK) are prevalent skin conditions with significant health complications. The molecular mechanisms underlying these conditions and their potential shared pathways remain ambiguous despite their prevalence. Therefore, this study aims to elucidate the common molecular pathways and potential therapeutic targets for BCC and AK through comprehensive computational network analysis. Linkage analysis was performed to identify common liable genes between BCC and AK. Protein-protein interactions (PPIs), Topological properties, GO enrichment, pathway enrichment, and gene regulatory network analyses were also performed to reveal potential molecular mechanisms and pathways. Furthermore, we evaluated protein-drug interactions (PDIs) to identify potential therapeutic targets. Our analysis revealed 22 common genes between BCC and AK: *TP53*, *EGFR*, *CDKN2A*, *MMP9*, *PTGS2*, *VDR*, *BCL2*, *MMP2*, *EZH2*, *TP63*, *FOXP3*, *MSH2*, *MMP14*, *FLG*, *MC1R*, *CDKN2B*, *TIMP3*, *TYR*, *SOX10*, *IRF4*, *KRT17*, and *NID1*. PPI network analysis highlighted TP53 and EGFR as central hubs, validated using RNA-seq data. Co-expression and physical interaction analysis revealed a strong interplay between the common genes at the transcriptional and functional levels. GO analysis identified skin cancer-relevant terms: "skin development", "immune system development", and "response to radiation" as significantly enriched biological processes, while pathway enrichment analysis highlighted several cancer-related pathways enrichment. Gene regulatory network analysis revealed complex interactions between genes, miRNAs, and transcription factors, with *TP53*, *BCL2*, and *EGFR* playing central roles. PDI network analysis identified ibuprofen as a potential therapeutic agent targeting PTGS2 and BCL2, while other proteins VDR, MMP2, MMP9, and TYR showed interactions with multiple drugs. This computational analysis provides valuable insights into the shared molecular mechanisms of BCC and AK, revealing common pathways and potential therapeutic targets for developing novel treatment strategies and repurposing existing drugs for these prevalent skin cancers. Therefore, these findings may guide future research in understanding and developing targeted therapies for both conditions.

* Corresponding author.
E-mail addresses: shahin018mbstu@gmail.com, shahinbge@mbstu.ac.bd (S. Mahmud).

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1. Introduction

Basal cell carcinoma (BCC) and actinic keratoses (AK) are the most prevalent malignant neoplasms in humans, also known as skin cancer, and their incidence has risen over the past few decades [1,2]. Primarily, skin cancer is caused by mutations in the DNA of skin cells [3]. The mutations allow the cells to multiply out of control, resulting in cancer. Secondly, UV (ultraviolet) radiation from sunlight and tanning bed lights causes significant DNA damage in the top layer of skin cells, where skin cancer begins [4].

While histopathology mostly confirms the diagnosis, there are tumor simulators and basal cell carcinomas with deceptive clinical appearances [5]. Nowadays, the incidence of BCC is growing [6]. On the other hand, AK, also known as solar or senile keratosis, is epidermal dysplasia that grows on skin that has been exposed to the sun for an extended period, most generally on the forehead, bald head, face, neck, or arms, and it is the most common pre-cancerous infection of the skin [7,8]. AKs appear as pink to red gritty macules or papules on sun-damaged skin. Patients with a high number of AKs are more likely to develop skin cancer [9]. The prevalence rises with age, and AK was observed in 25.3 % of outpatients in general practice in a recent Swiss survey [10]. Recent studies have revealed a notable overexpression of several key genes, including *FOXO3a*, *ATM*, *P65*, *TNF-α,* and *PINK1*, in patients with basal cell carcinoma (BCC) induced by radiation. This overexpression is linked to crucial biological processes such as cellular senescence and apoptosis, which are essential for regulating cell life cycles and responses to stress [11]. Additionally, many of these genes exhibit interactions with central hub proteins TP53 and EGFR, suggesting that they may play significant roles in the molecular pathways that govern tumor development and progression in BCC [12]. Both BCC and AK are closely associated with exposure to UV radiation, a major risk factor for the development of these skin conditions [13–15].

This study aims to employ computational network analysis techniques to investigate the potential common molecular targets and signaling pathways shared between BCC and AK to identify novel therapeutic targets for the management of these prevalent skin conditions.

Therefore, this study first retrieved the genes associated with BCC and AK from the NCBI Genbank database, focusing only on human disease-related genes. The common genes between BCC and AK were then identified using a Venn diagram tool and validated using the DisGeNet database. Protein-protein interaction (PPI) networks were constructed using IMEx Interactome and the STRING database within the NetworkAnalyst 3.0 platform to examine the functional relationships among the common genes. Topological properties of the PPI network, including Closeness Centrality, Clustering Coefficient, Betweenness Centrality, and Topological Coefficient, were analyzed using Cytoscape and its Network Analyzer application. Gene ontology (GO) term analysis was performed using WebGestalt, while KEGG and Reactome pathway enrichment was analyzed and visualized with Enrichr. Co-expression and physical interaction analysis were carried out using GeneMANIA, and a gene regulatory network was constructed by integrating data from miRTarBase, TRRUST, and the TF-miRNA coregulatory interaction database in NetworkAnalyst 3.0. Finally, the protein-drug interaction analysis was also performed using the DrugBank database within the NetworkAnalyst platform. The graphical representation of this study has been presented in Fig. 1.

2. Materials and methods

2.1. Retrieval of genes from database

The genes associated with BCC and AK were retrieved from the NCBI Genbank database (https://www.ncbi.nlm.nih.gov/) [16]. Only the genes linked to the *Homo sapiens* species were included in the analysis. Genes were then categorized based on their known functions and roles in disease pathogenesis and retained for further investigation. The NCBI Gene database was chosen for its experimental and curated collection of gene information associated with specific diseases. This categorization allowed for the identification of genes directly responsible for human diseases, excluding those with indirect or unknown associations. This filtering

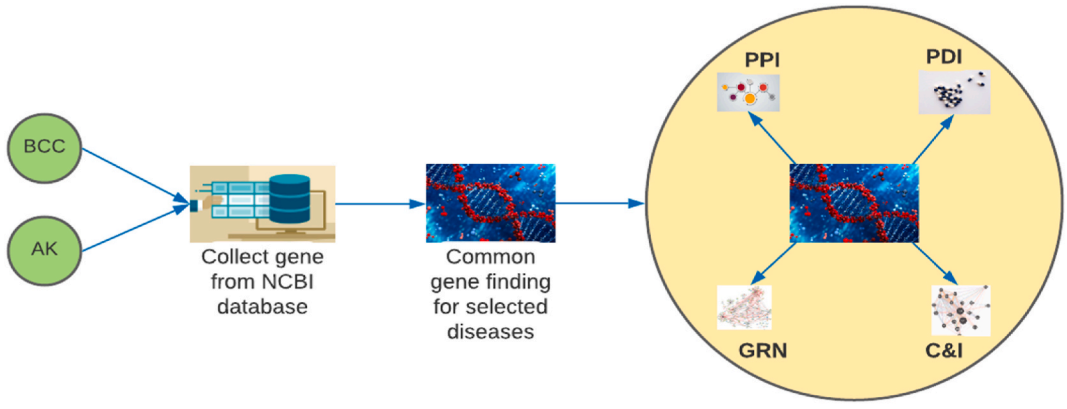


Fig. 1. Graphical representation of current study workflow where Protein-protein interactions (PPI), Gene Regulatory Network (GRN), Protein-drug interactions (PDI), Co-expression, and Physical Interactions (C&I) have been thoroughly analyzed.

process resulted in a refined list of genes directly implicated in BCC and AK, providing a focused dataset for investigation.

2.2. Data processing and validation

The common genes between BCC and AK were identified using a statistical test known as Fisher's exact test, which determined the significant association between genes of BCC and AK based on the sophisticated categorization technique [17]. Afterward, we utilized those associated genes to identify overlapping genes using the web-based Venn diagram tool available at https://bioinformatics.psb.ugent.be/webtools/Venn/ [18]. This tool allows users to upload gene lists or text files containing gene names and then calculates and visualizes the intersections between the provided lists. The symmetric Venn diagram option was selected to generate the graphical output of common genes between BCC and AK. Additionally, the identified common genes were further validated using the DisGeNet database (https://www.disgenet.com/), a comprehensive database of gene-disease associations, to ensure the relevance of these genes to skin cancer [19]. This two-step approach, combining the Venn diagram analysis and disease gene validation, enabled the identification of only the disease-relevant common skin cancer genes between BCC and AK.

2.3. Protein-protein interaction network analysis

The protein-protein interaction (PPI) network was constructed using the IMEx Interactome and STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) database within the NetworkAnalyst 3.0 platform (https://www.networkanalyst.ca/) [20]. IMEx Interactome utilizes literature-curated comprehensive data from InnateDB, while STRING is a database that provides details on predicted and known protein-protein connections, including direct (physical) and indirect (functional) interactions [21,22]. The highest confidence score (900) was used to analyze the STRING network. The use of IMEx Interactome and STRING on NetworkAnalyst 3.0 allowed for the comprehensive analysis of the PPI network, which is expected to provide insights into the functional relationships and interactions between the proteins of interest, thereby enhancing the understanding of the underlying biological processes and potential molecular mechanisms.

2.4. Examination of topological properties

The topological properties of the PPI network were analyzed using the Cytoscape software tool and its Network Analyzer application [23,24]. Cytoscape is a widely used open-source platform for visualizing, analyzing, and modeling complex networks. The Network Analyzer application within Cytoscape was utilized to calculate the topological metrics, including Closeness Centrality, Clustering Coefficient, Betweenness Centrality, and Topological Coefficient. These topological properties provide insights into the network structure and the importance of individual genes within the network. In particular, Betweenness Centrality determines the number of shortest paths that pass through a gene, Closeness Centrality evaluates how close a gene is to every other gene in the network, Clustering Coefficient shows how interconnected a gene's neighbors are, and Topological Coefficient shows how much a gene shares neighbors with other genes. Analyzing these topological features can help identify hub genes, which are genes that play a central role in the overall network and may represent potential therapeutic targets or biomarkers.

2.5. Exploration of Co-expression and physical interaction

Co-expression and physical interaction analysis were performed using GeneMANIA (https://www.genemania.org), a comprehensive online resource that integrates multiple data sources to predict functional relationships between genes and proteins [25]. GeneMANIA utilizes a network-based approach to analyze gene lists, identifying genes that are likely to be functionally related based on their co-expression patterns across various datasets, physical interactions, shared pathways, and other biological annotations to gain insights into the potential functional relationships between genes identified in our study, providing a broader context for understanding their roles in the biological processes.

2.6. Analysis of GO and pathway enrichment

The gene set enrichment analysis was conducted using two complementary web-based tools: WebGestalt (https://www.webgestalt.org/) and Enrichr (https://maayanlab.cloud/Enrichr/) [26,27]. WebGestalt provides a wide range of functionalities, including over-representation analysis, network analysis, and hierarchical clustering, to translate gene lists into biological insights. We selected Network Topology-based analysis (NTA) as the Method of Interest and network-based PPI BIOGRID as the Functional Database for *Homo sapiens* for responsible genes using the WeGestalt tool. The enriched GO terms Graphs are shown in Fig. 5. In contrast, the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Reactome pathways were analyzed using Enrichr. Enrichr offers a user-friendly interface and a diverse collection of gene set libraries, enabling efficient and comprehensive analysis of gene sets [28]. The use of these two complementary tools allowed for a thorough examination of the biological processes, pathways, and functional associations represented by the gene lists, providing a robust and well-rounded interpretation of the results.

2.7. Gene regulatory network analysis

To elucidate the gene regulatory network underlying the observed biological phenomenon, we employed again NetworkAnalyst

3.0. There are three types of gene regulatory networks: Gene-miRNA interaction, TF-gene interaction, and TF-miRNA co-regulatory network [29,30]. This tool facilitated the construction of a regulatory network by integrating three distinct datasets: Gene-miRNA interactions from miRTarBase v9.0, Gene-Transcription Factors (TFs) interactions from the TRRUST database, and miRNA-TF interactions from the TF-miRNA coregulatory interaction database [31–33]. The miRTarBase v9.0 database provides a curated repository of experimentally validated miRNA-target interactions, enabling us to identify potential regulatory relationships between miRNAs and genes. The TRRUST database, a comprehensive collection of experimentally validated TF-target interactions, allowed us to map the regulatory influence of TFs on gene expression. Finally, the TF-miRNA coregulatory interaction database provided insights into the intricate interplay between TFs and miRNAs in regulating gene expression.

2.8. Exploration of protein drug interaction networks

The protein-drug interaction analysis was also conducted using NetworkAnalyst 3.0. The DrugBank database, a comprehensive resource for information on drugs and their target proteins, was utilized as the data source for this analysis [34]. NetworkAnalyst 3.0 was selected as it provides a robust and user-friendly platform for exploring the complex relationships between proteins and their interacting drugs. The tool enables the construction of interaction networks, allowing for the identification of key proteins and their associated drugs, as well as the exploration of the underlying mechanisms of these interactions. By utilizing these tools, we aimed to identify potential drug targets and understand the molecular mechanisms underlying drug-protein interactions, thereby providing insights into the therapeutic potential of the investigated drugs. Fig. 6 depicts the entire list of medications that can be used to treat the above mentioned skin cancers.

2.9. Validation of hub genes and therapeutic targets

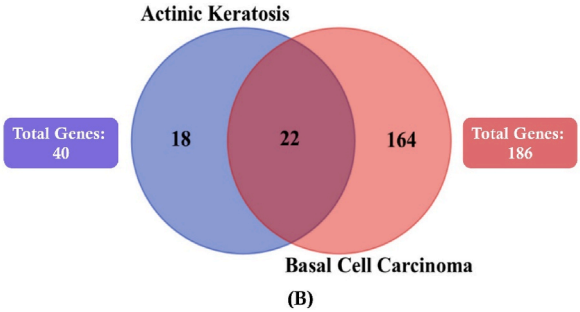
The hub genes often participate as therapeutic targets and biomarker potentials that play a central role in co-expression, physical interactions, and pathways involvement for a particular condition or disease [35,36]. Therefore, the common and key hub genes between BCC and AK that were previously identified using topological centralities (degree centrality, betweenness centrality, closeness centrality, clustering coefficient, and topological coefficient), were finally validated using RNA-seq data from the GEO (Gene Expression Omnibus) database [37]. The GEO database is a comprehensive collection of publicly available gene expression data, enabling large-scale meta-analyses, validation of findings, and the identification of novel biological insights across diverse experimental conditions and organisms [38]. The GEO datasets of BCC (GSE125285 and GSE196292) and AK (GSE90643 and GSE32979) were collected and analyzed with GEO2R to identify common differentially expressed genes between BCC and AK and validate our hub genes.

2.10. Immune therapy opportunities

To provide more depth to this study, we have performed a literature mining at Google Scholar and PubMed to identify the latest immune therapies that are common between BCC and AK [39,40]. At first, we identified the latest immune treatment opportunities for BCC and AK separately and then identified the common immune treatment opportunities. The search terms used included "basal cell carcinoma immune therapy," "actinic keratosis immune therapy," and related keywords. The findings from the two separate searches were then compared to pinpoint the common immune treatment options between BCC and AK.

Fisher's Exact Test (Overlapping Genes)	BCC Genes	Not BCC Genes
AK Genes	22	23
Not AK Genes	191	0

(A)



(B)

Fig. 2. Identification and visualization of overlapping genes. (A) Identification of overlapping genes using Fisher's exact test. (B) Visualization of overlapping genes using Venn diagram which shows 22 common genes between Basal cell carcinoma and Actinic keratosis genes dataset.

3. Results

3.1. Gene collection, gene mining, linkage & common gene finding

The gene collection and mining process yielded 186 and 40 liable genes for BCC and AK, respectively, after processing and sorting the associated genes for *Homo sapiens*. Notably, our linkage analysis revealed 22 common liable genes between BCC and AK, including *TP53*, *EGFR*, *CDKN2A*, *MMP9*, *PTGS2*, *VDR*, *BCL2*, *MMP2*, *EZH2*, *TP63*, *FOXP3*, *MSH2*, *MMP14*, *FLG*, *MC1R*, *CDKN2B*, *TIMP3*, *TYR*, *SOX10*, *IRF4*, *KRT17*, and *NID1*. These overlapping genes were identified using Fisher's exact test which is presented in Fig. 2 (A). The Venn diagram analysis (Fig. 2(B)) illustrates the total number of genes and common genes, confirming the intersection of two diseases and highlighting the significance of these common genes in the pathogenesis of both BCC and AK.

3.2. Analysis of protein-protein interaction network

The analysis of PPI networks of common genes between BCC and AK from the IMEx interactome of the InnateDB and STRING databases reveals several key insights. Fig. 3(A and B) shows that the protein TP53 has the highest degree of centrality (659 and 256) across InnateDB and STRING databases respectively, indicating its central role as a highly connected hub and its importance in facilitating communication between other proteins in the network. Similarly, EGFR also exhibits a high degree (391 and 137) of centrality. Other proteins of note include EZH2, CDKN2A, TP63, and BCL2, which demonstrate relatively high degree centrality values, implying their significance in the PPI network. Overall, the centrality measures derived from the InnateDB and STRING databases provide a comprehensive understanding of the key players and their relative importance in the complex web of PPIs. Both databases exhibit almost a common protein network with varying degrees of centralities. All the values of centrality measures of both of the databases have been provided in the Supplementary File.

3.3. Topological properties assessment

The topological properties of the top 10 liability-exposed genes were analyzed to gain insights into their structural and functional roles within the PPI network. As shown in Table 1, the genes exhibited varying degrees of closeness centrality, clustering coefficient, and topological coefficient. The gene with the highest closeness centrality was TP53 (0.585), indicating that it is the most central and influential node in the network. This suggests that TP53 plays a critical role in mediating interactions and information flow within the network. In contrast, IRF4 had the lowest closeness centrality (0.343), implying a less central position in the network topology. The clustering coefficient, which measures the degree of interconnectedness among a gene's neighbors, was highest for PTGS2 (0.024) and lowest for IRF4 (0.0), revealing differences in the local connectivity of the genes. The topological coefficient, which reflects the extent of a gene's shared neighbors with other nodes, was highest for IRF4 (0.055) and lowest for TP53 (0.003), indicating variations in the gene's propensity to be a hub or a bridge between functional modules within the network (Table 1 and Fig. 4(A)–D).

3.4. Co-expression & physical interaction analysis

GeneMANIA analyzed PPIs between common genes and revealed a significant prevalence of co-expression (33.94 %) and physical interactions (27.90 %) among the identified protein pairs. This suggests a strong interplay between these proteins at both the

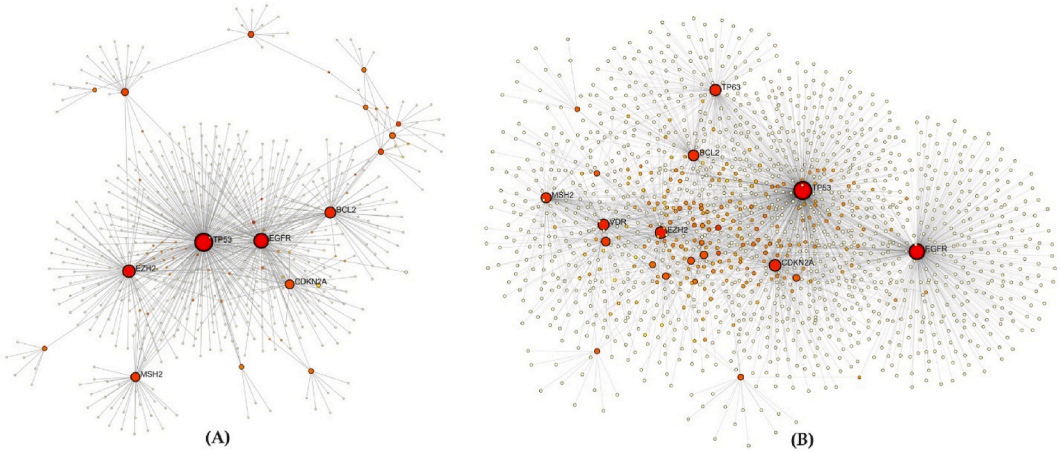


Fig. 3. Protein-Protein interaction network (A) InnateDB database and (B) STRING database using NetworkAnalyst 3.0 among common 22 genes to represent condensed interconnection where TP53, EGFR, BCL2, EZH2, MSH2, CDKN2A were the most common and significantly connected in both of the two databases.

Table 1
Using the Cytoscape tool, topological properties of the top 10 responsible genes from the PPI network were established.

Protein Name	Degree	Closeness Centrality	Clustering Coefficient	Betweenness Centrality	Topological Coefficient
TP53	659	0.585	0.001	0.618	0.003
EGFR	391	0.475	0.001	0.361	0.003
EZH2	149	0.369	0.002	0.106	0.013
CDKN2A	148	0.432	0.008	0.105	0.009
TP63	129	0.417	0.008	0.089	0.010
VDR	123	0.408	0.005	0.094	0.010
BCL2	114	0.405	0.006	0.081	0.011
MSH2	95	0.401	0.007	0.068	0.012
IRF4	60	0.343	0.000	0.051	0.055
PTGS2	39	0.393	0.024	0.020	0.029

transcriptional and functional levels. Pathway-based interactions account for 16.32 % of the total, while shared protein domains (9.16 %), predicted interactions (6.75 %), genetic interactions (5.06 %), and co-localization (0.87 %) make up the remaining categories. While pathway analysis and shared protein domains also contributed to our understanding of protein relationships, the prominence of co-expression and physical interactions highlights their importance in mediating protein function and network formation. Interestingly, the common genes: *TP53*, *EGFR*, *EZH2*, *MMP2*, *BCL2*, *MSH2*, *TYR*, and *TP63* were responsible for the pathway formation, and some new genes (*TYRP1*, *TIMP2*, and *PRDM1*) have also interacted with these common genes indicating these genes together may share a common pathway responsible for skin cancer development. The interacting networks also revealed that the functional consequence of these genetic interactions involved mostly in “response to light stimulus” (FDR: 1.21e-5), “response to UV” (FDR: 1.21e-5), and “melanosome” (FDR: 2.45e-5) which are common features responsible for skin cancers. The results of the co-expression and physical interaction analysis are presented in Table 2 and Fig. 5(A–D).

3.5. GO enrichment for common genes

The GO enrichment analysis identified several significantly enriched biological processes pertinent to skin cancer, with "gland development" (GO:0048732), "negative regulation of the cell cycle" (GO:0045786), and "response to oxidative stress" (GO:0006979) being notably enriched, with p-values of $3.2364e^{-8}$, $3.8675e^{-8}$ and $4.6365e^{-8}$, respectively, underscoring the potential role of these

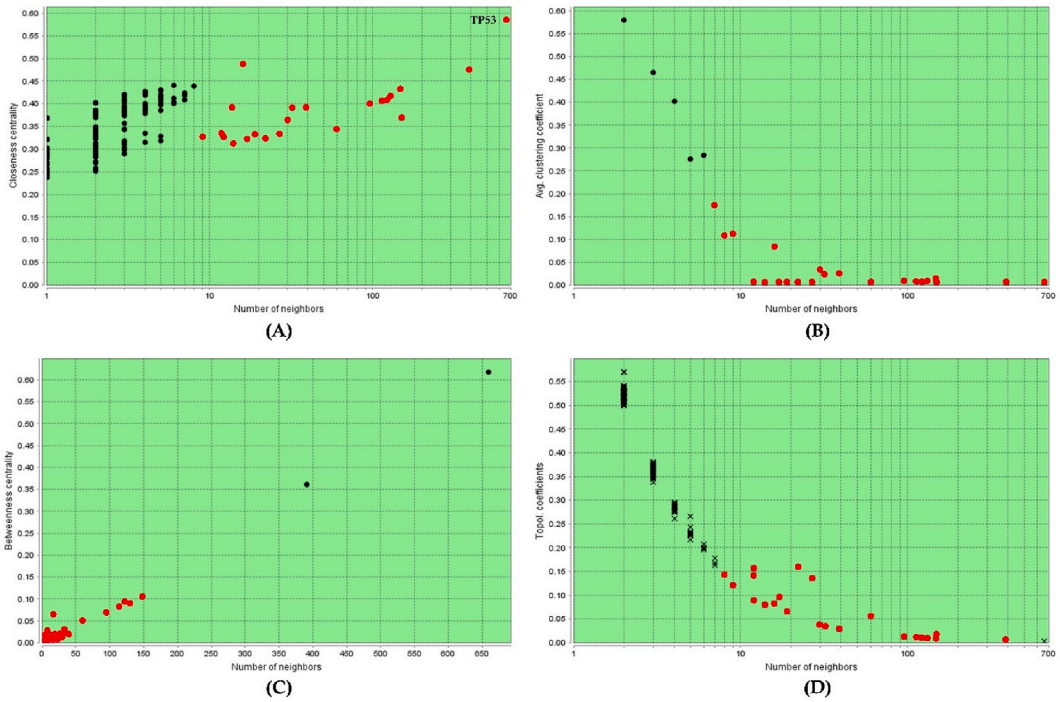


Fig. 4. Topological Properties of the top 22 responsible genes based on the PPI network. (A) represent the Closeness Centrality. (B) represent the avg. Cluster coefficient. (C) represent the Betweenness Centrality. (D) represent the Topological coefficient. The red dots represent the 22 genes together with highly connected neighbors (black) that have similar topological properties.

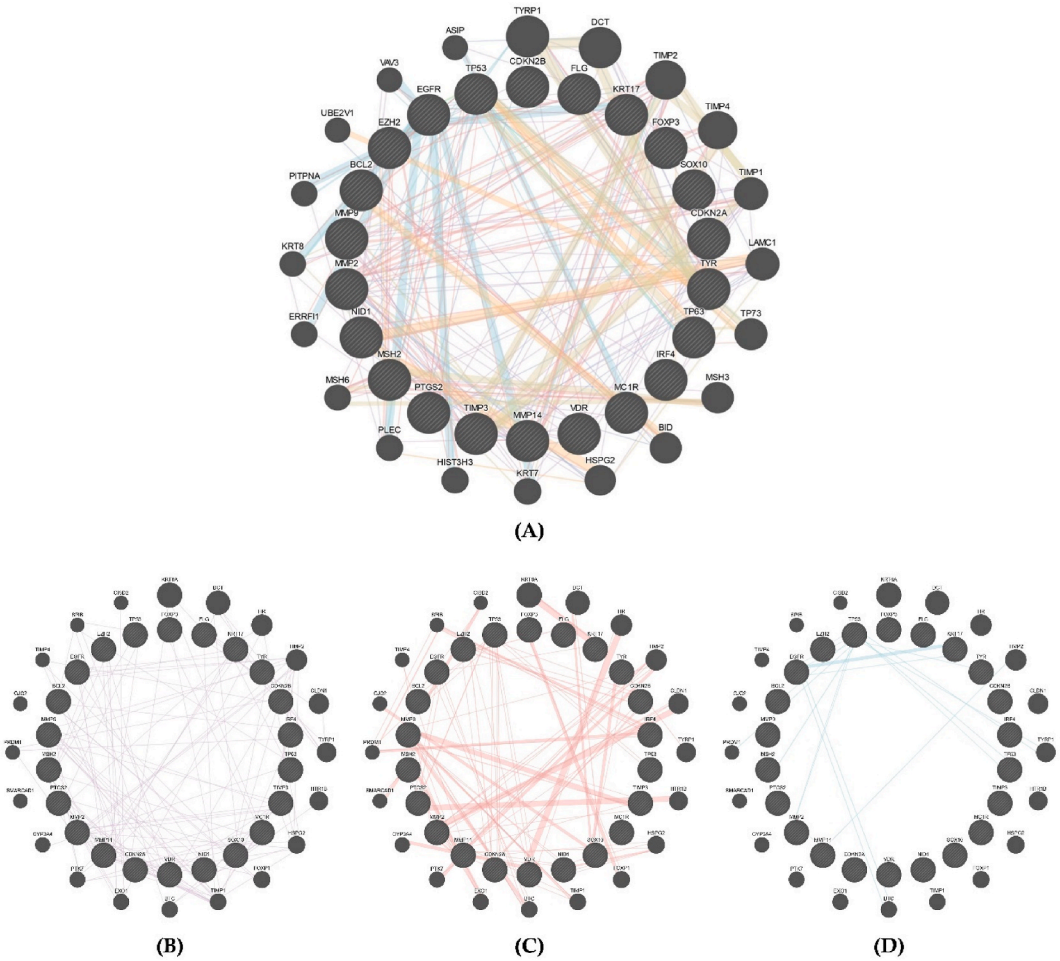


Fig. 5. Co-expression & Physical Interaction between 22 genes using GeneMANIA. (A) Whole network, (B) Co-expression, (C) Physical Interaction, (D) Pathway. Smaller size node represents a lower degree of association and larger node size represents a higher degree of association among genes.

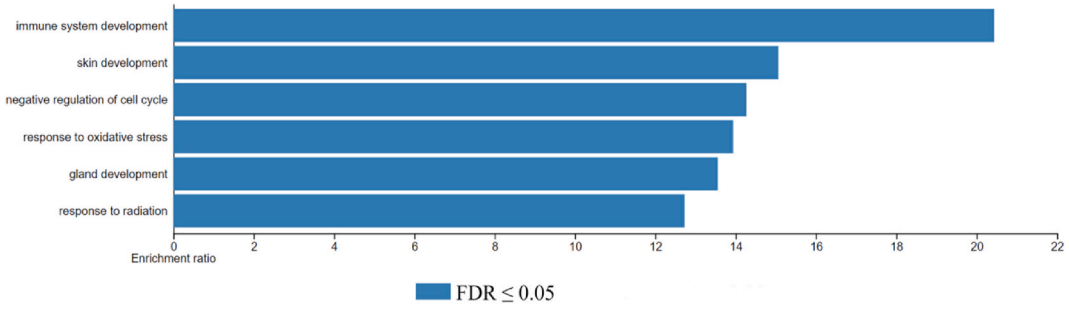


Fig. 6. Visualization of GO-terms enrichment analysis and their regulatory functions. 6 Major GO terms were significant with FDR ≤0.05.

processes in tumorigenesis. The term "response to radiation" (GO:0009314) also showed significant enrichment (p-value = $9.3524e^{-8}$), highlighting the genes' involvement in cellular responses to UV exposure, which is critical in skin cancer development. Furthermore, "skin development" (GO:0043588) and "immune system development" (GO:0002520) were enriched, with p-values of $2.2816e^{-7}$ and $3.2722e^{-7}$, respectively, suggesting that these biological processes may contribute to the pathophysiology of skin cancers through mechanisms related to tissue formation and immune response modulation. Hence, these findings shown in Fig. 6 are intricately linked to the mechanisms underlying skin cancer progression and response to environmental stressors. The False Discovery Rate (FDR) of all the terms was ≤0.05, suggesting the relevance and significance of these enrichments.

Table 2
Protein-protein interaction network analysis on GeneManina.

Category	Percentage
Co-expression	33.94 %
Physical Interactions	27.90 %
Pathway	16.32 %
Shared protein domains	9.16 %
Predicted	6.75 %
Genetic Interactions	5.06 %
Co-localization	0.87 %

3.6. Pathway enrichment for common genes

Pathway enrichment analysis revealed significant enrichment of genes associated with skin cancer in both KEGG and Reactome pathways. Fig. 7(A) represents the KEGG pathways implicated in skin cancer including microRNAs in cancer, Pathways in cancer, and Proteoglycans in cancer, suggesting a complex interplay of genetic and molecular mechanisms in skin cancer development. On the other hand, Reactome pathways, such as Intrinsic Pathway for Apoptosis, Extra-nuclear Estrogen Signaling, and Oxidative-Stress Induced Senescence were also enriched, highlighting the important role of apoptosis, estrogen signaling, and senescence in skin cancer progression shown in Fig. 7(B). Notably, the enrichment of Activation of Matrix Metalloproteinases and Degradation of Extracellular Matrix implicated tissue architecture and microenvironment disruption in skin cancer.

3.7. Gene regulatory network analysis

The gene regulatory network analysis revealed complex interactions between genes, miRNAs, and transcription factors (TFs) in the investigated system. Fig. 8 (A, B, and C) depict the gene-miRNA interaction, TF-gene interaction, and TF-miRNA co-regulatory network, respectively, with detailed information on interacting miRNAs and TFs provided in the Supplementary File. Notably, genes with significant interactions with miRNA in the network included *TP53*, *BCL2*, *VDR*, *EGFR*, *EZH2*, *MMP2*, *MMP9*, *IRF4*, *NID1*, *PTGS2*, *TIMP3*, *CDKN2B*, *CDKN2A*, *TP63*, *MMP14*, *FOXP3*, and *MSH2*. Furthermore, genes exhibiting a high degree of interaction with TFs (degree value > 10) were *TP53*, *BCL2*, *PTGS2*, *MMP9*, *MMP2*, *EGFR*, *CDKN2A*, *VDR*, *CDKN2B*, *MMP14*, and *EZH2*, suggesting their central roles in the regulatory network. These genes are primarily involved in cell cycle regulation, apoptosis, and DNA repair, suggesting their crucial roles in maintaining cellular homeostasis. The interactions between these genes and their regulators are significant for understanding the underlying mechanisms of cellular processes and disease development.

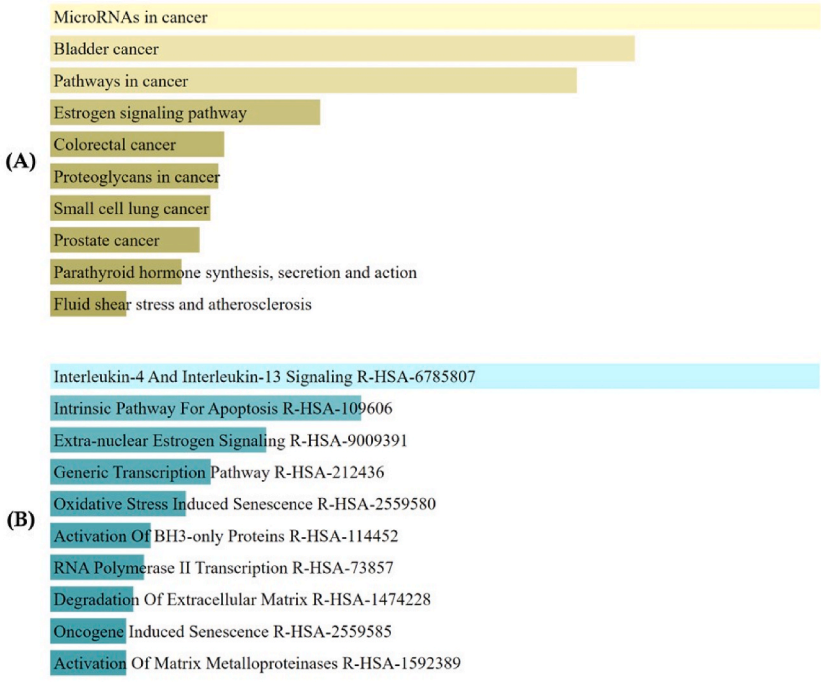


Fig. 7. Pathway analysis revealed (A) KEGG and (B) Reactome Pathways enrichment.

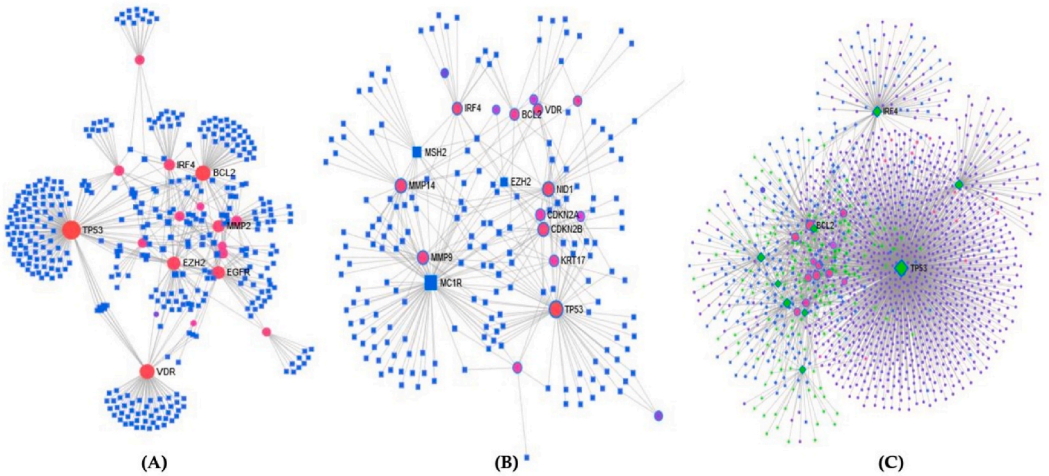


Fig. 8. Gene regulatory network analysis revealed (A) Gene-miRNA interaction, (B) TF-gene Interaction, and (C) TF-miRNA Coregulatory Network.

3.8. Protein-drug interaction network analysis

The protein-drug interaction network analysis presented in Fig. 9 revealed several key insights for skin cancer drug screening. Ibuprofen, a common anti-inflammatory drug, was found to interact with both PTGS2 and BCL2, which are known to play important roles in skin cancer progression. Additionally, the analysis identified several other proteins, including VDR, MMP2, MMP9, TYR, and MC1R, that interacted with multiple drugs, suggesting their potential as important targets for skin cancer therapy developed by BCC or AK. From manual observation of the DrugBank database and literature mining of Google Scholar and PubMed, we have gathered three more approved drugs: fluorouracil, imiquimod, and aminolevulinic acid that are common between BCC and AK and, therefore, could also be promising for the treatment of these skin cancers apart from ibuprofen [41–43]. This comprehensive network analysis provides

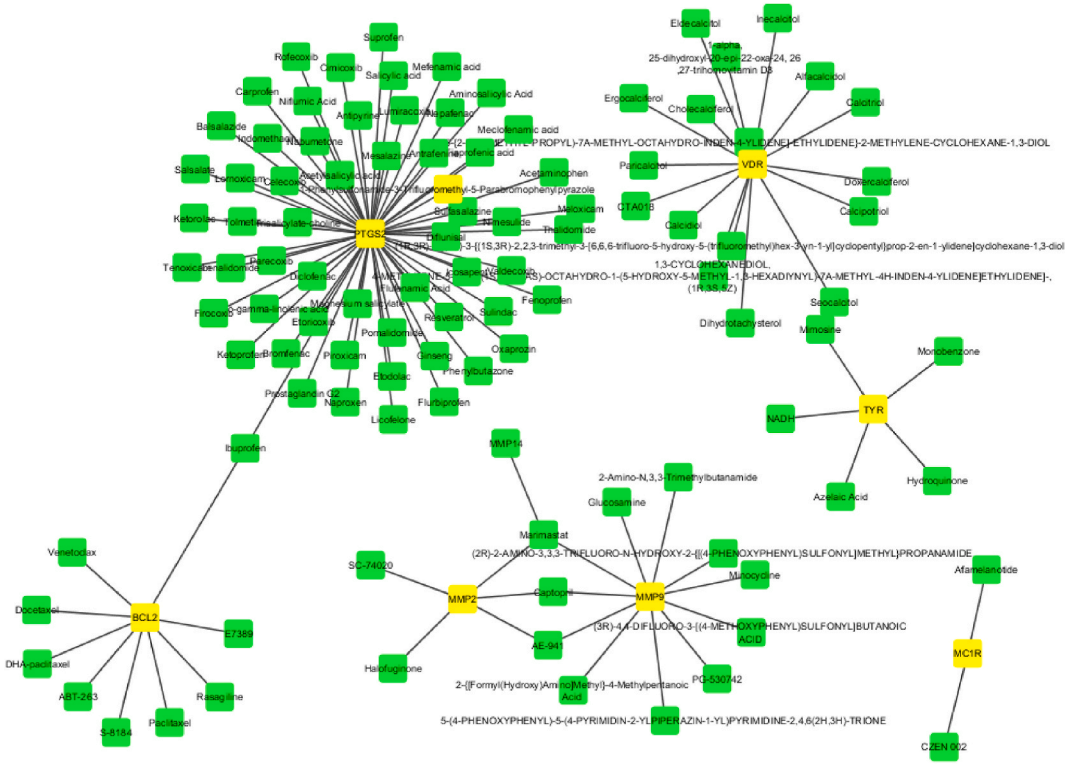


Fig. 9. Graphical representation of PDI network using Networkanalyst where PTGS and BCL2 interacted with common drug ibuprofen. Multiple other drugs interacted with proteins VDR, MMP2, MMP9, TYR, and MC1R.

a valuable framework for identifying and prioritizing drug candidates that can simultaneously target multiple critical pathways involved in skin cancer development and progression, potentially leading to more effective treatment strategies. Hence, these findings underscore the interconnected nature of drug-protein interactions and offer insights into potential drug repurposing opportunities. The complete list of drug-protein interactions has been provided in the Supplementary File.

3.9. Validated hub genes with skin cancer therapeutic opportunities

Following the removal of duplicates, a total of 11,649 and 12,977 differentially expressed genes were obtained for basal cell carcinoma (BCC) and actinic keratosis (AK) microarray datasets, respectively. Notably, seven of the initially identified top 10 hub genes were found to be dysregulated in both BCC and AK skin cancers, including *EGFR*, *MSH2*, *EZH2*, *CDKN2A*, *VDR*, *TP53*, and *BCL2*. Among these, *EGFR* and *BCL2* were upregulated in both BCC and AK, while *MSH2*, *EZH2*, *CDKN2A*, *VDR*, and *TP53* were down-regulated in both conditions. The adjusted p-value <0.05 was considered statistically significant. These seven key hub genes are most likely involved in the pathogenesis of skin cancer through the shared pathways of BCC and AK. Dysregulated genes and seven validated hub genes have been shown in Fig. 10(A–C). Furthermore, these validated hub proteins have been considered promising therapeutic targets for the treatment of these skin cancers. Consistent with this, we have previously validated and visualized BCL2 as a therapeutic target in a protein-drug interaction network (Fig. 9). The compiled list of RNA-seq data for BCC and AK is provided in Supplementary File 2.

3.10. Common immune therapy opportunities

The findings from the literature demonstrate promising opportunities for common immune therapy approaches in the treatment of basal cell carcinoma (BCC) and actinic keratosis (AK). The immune response modifier imiquimod, which induces cytokine production and stimulates both innate and adaptive immune pathways, is an approved and widely utilized treatment option for these conditions [44]. Additionally, the human monoclonal antibody cemiplimab has been shown to enhance anti-tumor T-cell responses, thereby modulating anti-cancer activities, and has demonstrated efficacy against both BCC and AK [45–47]. Both therapeutic agents showed clinical effectiveness in managing BCC and AK, suggesting the viability of immune-based approaches in treating these dermatological conditions.

4. Discussion

This study aimed to identify common molecular mechanisms of BCC And AK and provides several insights into central proteins TP53 and EGFR, biological processes, and, involvement in pathways to regulate skin cancers.

TP53, a tumor suppressor gene, is critical in regulating the cell cycle, DNA repair, and apoptosis [48,49]. Mutations in *TP53* are commonly associated with various cancers, including skin cancers like Basal Cell Carcinoma (BCC) and Actinic Keratosis (AK) [42,50]. Its centrality in cellular processes makes it a crucial target for cancer therapies aimed at restoring normal regulatory functions. On the other hand, *EGFR* is a receptor tyrosine kinase that, when activated, triggers a cascade of signaling pathways involved in cell proliferation, survival, and differentiation [51]. Overexpression or mutations in *EGFR* are frequently implicated in various cancers, including skin cancer [52]. Targeting EGFR protein has become a central strategy in cancer therapy, particularly in promoting tumor growth and metastasis.

Initially, our study identified 22 common genes between the two cancers BCC and AK (*TP53*, *EGFR*, *CDKN2A*, *MMP9*, *PTGS2*, *VDR*, *BCL2*, *MMP2*, *EZH2*, *TP63*, *FOXP3*, *MSH2*, *MMP14*, *FLG*, *MC1R*, *CDKN2B*, *TIMP3*, *TYR*, *SOX10*, *IRF4*, *KRT17*, and *NID1*), suggesting shared pathogenic mechanisms and potential common therapeutic targets for both BCC and AK.

Analysis of PPI networks revealed TP53 and EGFR as central hub proteins with high degrees of centrality. Other highly connected proteins (EZH2, CDKN2A, TP63, BCL2) further emphasize their importance in the disease processes. Furthermore, analysis of topological properties (closeness centrality, clustering coefficient, topological coefficient) of the top 10 liability genes provided further insights into their roles within the PPI network, where again TP53 and EGFR showed the highest centrality, indicating its central role in mediating interactions. The hub proteins were validated using RNA-seq data. Additionally, GeneMANIA analysis revealed a high prevalence of co-expression (33.94 %) and physical interactions (27.90 %) among the common genes, indicating strong interplay at both transcriptional and functional levels. This strengthens the biological relevance of the identified gene network.

GO enrichment analysis revealed significant enrichment of terms related to gland development, cell cycle regulation, response to oxidative stress, response to radiation, and skin development. These findings underscore the involvement of these processes in BCC and AK pathogenesis. KEGG and Reactome pathway enrichment revealed significant involvement of pathways related to cancer, apoptosis, estrogen signaling, senescence, and extracellular matrix degradation, pointing to the complex interplay of multiple pathways in the development and progression of BCC and AK.

Gene regulatory networks showed complex interactions between genes, microRNAs (miRNAs), and transcription factors (TFs). Key genes (*TP53*, *BCL2*, *EGFR*, etc.) showed significant interactions with miRNAs and TFs, highlighting their central roles in regulating cellular processes relevant to skin cancer. PDI network analysis identified potential drug targets for both BCC and AK. The interaction of ibuprofen with PTGS2 and BCL2 suggests potential for drug repurposing opportunities. Other drugs, fluorouracil, imiquimod, and aminolevulinic acid, interacted with both BCC and AK identified through literature mining, have else the potential for drug repurposing for the treatment of skin cancers, highlighting the potential for developing novel skin cancer therapies targeting multiple pathways simultaneously. Apart from chemotherapy, the efficacy of imiquimod and cemiplimab in treating BCC and AK underscores

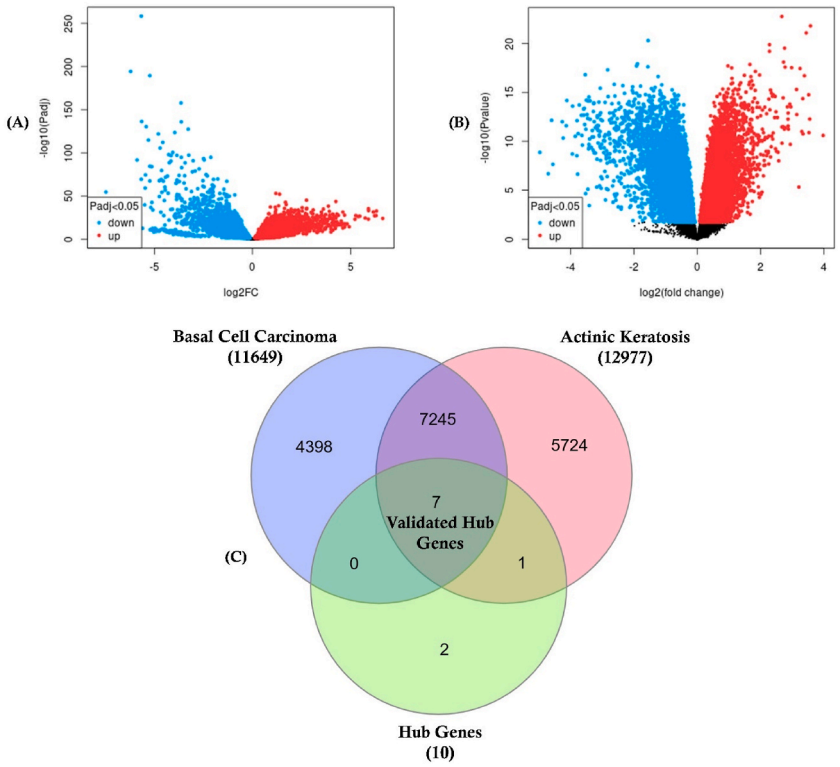


Fig. 10. Validation of hub genes from GEO datasets. (A) and (B) Significantly upregulated and downregulated genes of BCC and AK, respectively. (C) Seven validated hub genes of topological centralities using dysregulated genes of BCC, and AK from RNA-seq data.

the potential of immune-based therapies for common dermatological conditions, which further strengthens our study on the association between BCC and AK on skin cancer treatment.

This integrated approach provides a more holistic understanding of the shared genetic mechanisms underlying BCC and AK than previous studies, which often focused on individual genes or pathways [11,53,54]. The identification of common genes and pathways offers a potential for developing more effective and targeted therapies for both diseases. Therefore, future research should focus on experimental validation of the identified genes using in vitro and in vivo models and identify clinical relevance of the identified protein-drug interactions.

5. Conclusion

This research provides an overview of two types of skin cancer: BCC and AK. PPI and PDI, two of the most significant features, have also been thoroughly examined in this study to elucidate the molecular mechanisms underlying BCC and AK. Our comprehensive analysis revealed a set of 22 common genes between BCC and AK, which are interconnected through a complex network of protein-protein interactions, co-expression, and regulatory relationships. Notably, TP53 and EGFR emerged as central hubs in the PPI network, while functional enrichment analysis highlighted the importance of skin development, immune system development, response to radiation, and several cancer pathways in the pathogenesis of both conditions. Furthermore, our analysis identified ibuprofen as a potential therapeutic agent targeting PTGS2 and BCL2 and revealed multiple drug interactions with VDR, MMP2, MMP9, TYR, and MC1R. These findings provide a rich resource for understanding the shared molecular mechanisms of BCC and AK and offer promising avenues for developing novel therapeutic strategies and repurposing existing drugs for these debilitating skin cancers. Ultimately, our study demonstrates the power of computational network analysis in illuminating the complex biology of human disease and informing the developmental strategies of targeted therapies.

CRediT authorship contribution statement

Md Sujan Mahmud: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Bikash Kumar Paul:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Md. Rakibul Hasan:** Validation, Methodology, Formal analysis, Data curation. **K.M. Tanjida Islam:** Writing – original draft, Validation, Methodology, Formal analysis, Data curation. **Imran Mahmud:** Writing – review & editing, Validation, Methodology, Formal analysis. **Shahin Mahmud:** Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Conceptualization.

Data availability statement

Data included in the article/supplementary material is referenced in the article.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviation:

NCBI = National Center for Biotechnology Information
BCC = Basal cell Carcinoma
AK = Actinic keratosis
PPI = Protein-protein interaction
GRN = Gene regulatory network
PDI = Protein-drug interaction
TFs = Transcription Factors
GO = Gene Ontology
KEGG = Kyoto Encyclopedia of Genes and Genomes
FDR False Discovery Rate
GEO = Gene Expression Omnibus

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e41688.

References

[1] N.H. Cox, Fitzpatrick's dermatology in general medicine, Br. J. Dermatol. 150 (4) (2004), https://doi.org/10.1111/j.1365-2133.2004.6032_1.x.
[2] P. Chetty, F. Choi, T. Mitchell, Primary Care Review of Actinic Keratosis and its Therapeutic Options: A Global Perspective, 2015, https://doi.org/10.1007/s13555-015-0070-9.
[3] J. Schierbeck, T. Vestergaard, A. Bygum, Skin cancer associated genodermatoses: a literature review, Acta Derm. Venereol. 99 (4) (2019), https://doi.org/10.2340/00015555-3123.
[4] U. Leiter, U. Keim, C. Garbe, Epidemiology of skin cancer: update 2019, Adv. Exp. Med. Biol. 1268 (2020), https://doi.org/10.1007/978-3-030-46227-7_6.
[5] U. Wollina, J. Schönlebe, G. Tchernev, A.A. Chokoeva, T. Lotti, Basal cell carcinoma or not Basal cell carcinoma? That is the question, J. Biol. Regul. Homeost. Agents 29 (1) (2015) 1.
[6] E. Ng, J. Dong, D. Ratner, Basal Cell Carcinoma, Evidence-based procedural dermatology, 2019, pp. 723–748.
[7] T. Rosen, M.G. Lebwohl, Prevalence and awareness of actinic keratosis: barriers and opportunities, J. Am. Acad. Dermatol. 68 (1) (2013) S2–S9.
[8] W.D. James, E.D.M. BergerTG, Epidermal nevi, neoplasm and cysts. Andrews's diseases of the skin, Clin. Dermatol. (2011) 634–635.
[9] A. Pye, D. Wallis, V. Mishra, Actinic keratosis, A Practical Guide to Skin Cancer (2018) 21–33.
[10] J. Röwert-Huber, et al., Actinic keratosis is an early in situ squamous cell carcinoma: a proposal for reclassification, Br. J. Dermatol. 156 (s3) (2007) 8–12.
[11] R. Jenni, et al., Differential expression of ATM, NF-KB, PINK1 and Foxo3a in radiation-induced basal cell carcinoma, Int. J. Mol. Sci. 24 (8) (2023) 7181.
[12] S. Esmaeili, N. Faraji, S. Bahrami, S. Shaddeli, A. Ahmadi, B. Mostafaei, Deep excision surgery of face due to cruel invasion of basal cell carcinoma: a case report study, Int J Surg Case Rep 109 (2023) 108551.
[13] Y. Teng, et al., Ultraviolet radiation and basal cell carcinoma: an environmental perspective, Front. Public Health 9 (2021) 666528.
[14] B. Berman, C.J. Cockerell, Pathobiology of actinic keratosis: ultraviolet-dependent keratinocyte proliferation, J. Am. Acad. Dermatol. 68 (1) (2013) S10–S19.
[15] A. Traianou, et al., Risk factors for actinic keratosis in eight European centres: a case–control study, Br. J. Dermatol. 167 (s2) (2012) 36–42.
[16] E.W. Sayers, et al., GenBank, Nucleic Acids Res. 50 (D1) (2022) D161–D164.
[17] D.R. de Lima Cabral, R.S.M. de Barros, Concept drift detection based on Fisher's Exact test, Inf. Sci. 442 (2018) 220–234.
[18] A. Jia, L. Xu, Y. Wang, Venn diagrams in bioinformatics, Brief Bioinform 22 (5) (2021) bbab108.
[19] J. Piñero, et al., The DisGeNET knowledge platform for disease genomics: 2019 update, Nucleic Acids Res. 48 (D1) (2020) D845–D855.
[20] G. Zhou, O. Soufan, J. Ewald, R.E.W. Hancock, N. Basu, J. Xia, NetworkAnalyst 3.0: a visual analytics platform for comprehensive gene expression profiling and meta-analysis, Nucleic Acids Res. 47 (W1) (2019) W234–W241.
[21] K. Breuer, et al., InnateDB: systems biology of innate immunity and beyond—recent updates and continuing curation, Nucleic Acids Res. 41 (D1) (2013) D1228–D1233.
[22] D. Szklarczyk, et al., STRING v10: protein–protein interaction networks, integrated over the tree of life, Nucleic Acids Res. 43 (D1) (2015) D447–D452.

[23] M.S. Cline, et al., Integration of biological networks and gene expression data using Cytoscape, Nat. Protoc. 2 (10) (2007) 2366–2382.
[24] R. Saito, et al., A travel guide to Cytoscape plugins, Nat. Methods 9 (11) (2012) 1069–1076.
[25] M. Franz, et al., GeneMANIA update 2018, Nucleic Acids Res. 46 (W1) (2018) W60–W64.
[26] Y. Liao, J. Wang, E.J. Jaehnig, Z. Shi, B. Zhang, WebGestalt 2019: gene set analysis toolkit with revamped UIs and APIs, Nucleic Acids Res. 47 (W1) (2019) W199–W205.
[27] M.V. Kuleshov, et al., Enrichr: a comprehensive gene set enrichment analysis web server 2016 update, Nucleic Acids Res. 44 (W1) (2016) W90–W97.
[28] E.Y. Chen, et al., Enrichr: interactive and collaborative HTML5 gene list enrichment analysis tool, BMC Bioinf. 14 (2013) 1–14.
[29] H.E. Arda, A.J.M. Walhout, Gene-centered regulatory networks, Brief Funct Genomics 9 (1) (2010) 4–12.
[30] E. Gov, K.Y. Arga, Interactive cooperation and hierarchical operation of microRNA and transcription factor crosstalk in human transcriptional regulatory network, IET Syst. Biol. 10 (6) (2016) 219–228.
[31] G. Skoufos, et al., TarBase-v9. 0 extends experimentally supported miRNA–gene interactions to cell-types and virally encoded miRNAs, Nucleic Acids Res. 52 (D1) (2024) D304–D310.
[32] H. Han, et al., TRRUST v2: an expanded reference database of human and mouse transcriptional regulatory interactions, Nucleic Acids Res. 46 (D1) (2018) D380–D386.
[33] Z. Tong, Q. Cui, J. Wang, Y. Zhou, TransmiR v2. 0: an updated transcription factor-microRNA regulation database, Nucleic Acids Res. 47 (D1) (2019) D253–D258.
[34] C. Knox, et al., DrugBank 6.0: the DrugBank knowledgebase for 2024, Nucleic Acids Res. 52 (D1) (2024) D1265–D1275.
[35] P.F. Zheng, L.Z. Chen, Y.Z. Guan, P. Liu, Weighted gene co-expression network analysis identifies specific modules and hub genes related to coronary artery disease, Sci. Rep. 11 (1) (Mar. 2021) 1–13, https://doi.org/10.1038/s41598-021-86207-0, 2021 11:1.
[36] A. Hasankhani, et al., Differential Co-expression network analysis reveals key hub-high traffic genes as potential therapeutic targets for COVID-19 pandemic, Front. Immunol. 12 (Dec. 2021) 789317, https://doi.org/10.3389/FIMMU.2021.789317/BIBTEX.
[37] E. Clough, et al., NCBI GEO: archive for gene expression and epigenomics data sets: 23-year update, Nucleic Acids Res. 52 (D1) (Jan. 2024) D138–D144, https://doi.org/10.1093/NAR/GKAD965.
[38] Y. Jin, H. Wang, Identification of hub genes affecting gestational diabetes mellitus based on GEO database, Biotechnol. Genet. Eng. Rev. (Nov. 2024), https://doi.org/10.1080/02648725.2023.2215966.
[39] M. Gusenbauer, N.R. Haddaway, Which academic search systems are suitable for systematic reviews or meta-analyses? Evaluating retrieval qualities of Google Scholar, PubMed, and 26 other resources, Res. Synth. Methods 11 (2) (2020) 181–217.
[40] J. White, PubMed 2.0, Med. Ref. Serv. Q. 39 (4) (2020) 382–387.
[41] D. Arcuri, et al., Pharmacological agents used in the prevention and treatment of actinic keratosis: a review, Int. J. Mol. Sci. 24 (5) (2023) 4989.
[42] I.J. Tan, G.N. Pathak, F.H. Silver, Topical treatments for basal cell carcinoma and actinic keratosis in the United States, Cancers 15 (15) (2023) 3927.
[43] A.S. Farberg, J.W. Marson, T. Soleymani, Advances in photodynamic therapy for the treatment of actinic keratosis and nonmelanoma skin cancer: a narrative review, Dermatol. Ther. 13 (3) (2023) 689–716.
[44] E. Hanna, R. Abadi, O. Abbas, Imiquimod in dermatology: an overview, Int. J. Dermatol. 55 (8) (2016) 831–844.
[45] E.-C. Cozma, L.M. Banciu, C. Soare, S.-M. Cretoiu, Update on the molecular pathology of cutaneous squamous cell carcinoma, Int. J. Mol. Sci. 24 (7) (2023) 6646.
[46] T.S. Win, H. Tsao, Keratinocytic skin cancers—update on the molecular biology, Cancer 129 (6) (2023) 836–844.
[47] L. Ungureanu, et al., Immunotherapy in basal cell carcinoma, J. Clin. Med. 13 (19) (2024) 5730.
[48] A.F. Thomas, G.L. Kelly, A. Strasser, Of the many cellular responses activated by TP53, which ones are critical for tumour suppression? Cell Death Differ. 29 (5) (2022) 961–971.
[49] H. Wang, M. Guo, H. Wei, Y. Chen, Targeting p53 pathways: mechanisms, structures, and advances in therapy, Signal Transduct Target Ther 8 (1) (2023) 92.
[50] K. Wunderlich, M. Suppa, S. Gandini, J. Lipski, J.M. White, V. Del Marmol, Risk factors and innovations in risk assessment for melanoma, basal cell carcinoma, and squamous cell carcinoma, Cancers 16 (5) (2024) 1016.
[51] M.E. Bahar, H.J. Kim, D.R. Kim, Targeting the RAS/RAF/MAPK pathway for cancer therapy: from mechanism to clinical studies, Signal Transduct Target Ther 8 (1) (2023) 455.
[52] C. Tomuleasa, et al., Therapeutic advances of targeting receptor tyrosine kinases in cancer, Signal Transduct Target Ther 9 (1) (2024) 201.
[53] S. Ulutas, M. Mutaf, M.N. Koc, T. Oztuzcu, M. Ulasli, S. Oztuzcu, High-throughput screening and clinical importance of autophagy-associated genes in basal cell carcinoma, Pathol. Res. Pract. 250 (2023) 154786.
[54] Z. Wang, et al., Advancements in elucidating the pathogenesis of actinic keratosis: present state and future prospects, Front. Med. 11 (2024) 1330491.