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NETWORK-BASED FUNCTIONAL AND PATHWAY ANALYSIS OF MELANOMA-ASSOCIATED GENES USING BIOINFORMATICS APPROACHES

Nitesh Singh* and Jiya Prajapati

Department of Biotechnology,

Pillai College of Arts, Commerce & Science (Empowered Autonomous),

New Panvel, Navi Mumbai, Maharashtra

**Corresponding author E-mail: niteshsingh@mes.ac.in*

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Abstract:

Melanoma is one of the most aggressive forms of skin cancer, characterized by rapid progression, high metastatic potential, and increasing global incidence. Understanding the molecular mechanisms underlying melanoma is essential for improving diagnosis, prognosis, and targeted therapy. The present study employed a network-based bioinformatics approach to investigate melanoma-associated genes and their functional roles in disease progression. Melanoma-related genes were first identified from publicly available gene–disease association databases and curated based on their relevance and association strength. A set of 30 significant genes was selected for further analysis. Protein–protein interaction (PPI) network construction was performed to explore the functional relationships among these genes and to identify key hub genes involved in melanoma development. Gene interaction network expansion was conducted to evaluate functional connectivity and co-expression patterns. Functional and pathway enrichment analyses were subsequently carried out to determine the biological processes and signaling pathways associated with the selected genes. The results revealed strong enrichment in pathways related to MAPK signaling, cell proliferation, apoptosis regulation, immune response, and melanogenesis. Several hub genes, including key oncogenes and tumor suppressor genes, were found to play central roles in melanoma progression. Overall, this study highlights the importance of integrated bioinformatics analysis in understanding complex disease mechanisms and identifying potential biomarkers and therapeutic targets for melanoma.

Keywords: *Melanoma, Bioinformatics, Protein–Protein Interaction Network, Gene Interaction Network, Pathway Enrichment Analysis, MAPK Signaling, Hub Genes, Cancer Genomics.*

Introduction

Melanoma is the most highly malignant type of skin cancer and is characterized by lymphatic and hematogenous metastasis, which is directed in proportion to the vertical depth invasion of tumor cells into skin (1). The global incidence of melanoma has increased significantly over recent decades, posing a major public health concern. At the molecular level, melanoma is characterized by complex genetic alterations affecting cell proliferation, survival, differentiation, and immune regulation The World Health Organization (WHO) reports that melanoma accounts for nearly 132,000 new cases worldwide each year, and its incidence continues to rise at an annual rate of 2–3%. Early-stage melanoma can be successfully treated through complete surgical excision; however, late diagnosis frequently results in disease progression and poor prognosis. In metastatic melanoma, patient survival is typically limited to 6–9 months. The high incidence rate, difficulties in early detection, and rapid metastatic progression highlight the importance of melanoma as a major subject of scientific study. According to the National Cancer Institute of the National Institutes of Health (NIH), melanoma arises from the malignant transformation of melanocytes, the specialized cells responsible for the synthesis of melanin, the pigment that determines skin color. Melanoma most commonly develops on sun-exposed areas of the skin, although it may also occur in less visible sites such as the eyes, nasal passages, and throat. While the precise etiology of melanoma remains unclear, exposure to ultraviolet (UV) radiation from natural sunlight and artificial sources, including tanning beds, is considered a major risk factor. Individuals exposed to prolonged or intense UV radiation have an increased risk of developing melanoma, as excessive sun exposure can induce skin pigmentation changes and DNA damage. In this context, several plant-derived compounds have been investigated for their potential roles in modulating melanin synthesis and protecting against UV-induced skin damage. Melanoma is most frequently diagnosed in individuals aged 45 years and above and is characterized by a high metastatic potential. The disease often progresses silently without noticeable symptoms, which contributes to delayed diagnosis and underscores the importance of early detection. When identified at an early stage, melanoma can be effectively treated, significantly improving patient outcomes.

The World Health Organization (WHO) recognizes melanoma as one of the most common cancers of endocrine origin. Although historically prevalent in Western populations, recent data from the Global Cancer Observatory report more than 10,000 new cases in Asia in 2020, suggesting a rising incidence in non-Western countries. Climate change–associated increases in ultraviolet (UV) radiation exposure may further contribute to this growing burden. Melanoma occurs more frequently in men than women, with men over 50 years of age at particularly high risk. In 2020, melanoma accounted for over 52,000 deaths worldwide. The management of melanoma involves surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapeutic approaches. FDA-approved drugs such as nivolumab and relatlimab have improved outcomes, and early diagnosis can increase five-year survival rates from approximately 5% to 50%. However, melanoma frequently relapses due to resistance to apoptosis. Recent studies suggest that combining conventional therapies with natural products used in Traditional Chinese and Korean Medicine may reduce side effects, overcome drug resistance, and improve patient quality of life. These findings highlight the need for continued research into alternative and adjuvant therapeutic strategies for melanoma (2).

In recent years, bioinformatics has emerged as a powerful and indispensable approach in cancer research, particularly for understanding complex diseases such as melanoma. High-throughput technologies generate large

volumes of genomic and proteomic data, which cannot be efficiently analysed using conventional experimental methods alone. Bioinformatics tools enable the systematic analysis of such data to identify disease-associated genes, molecular interactions, and dysregulated biological pathways involved in melanoma development and progression.

Network-based bioinformatics approaches, such as protein–protein interaction (PPI) network analysis, provide insights into the functional relationships among melanoma-associated genes and help identify key hub genes that play central roles in tumor growth, metastasis, and immune regulation. Additionally, functional enrichment and pathway analyses allow the identification of significantly enriched biological processes and signaling pathways, including MAPK/ERK signaling, apoptosis regulation, cell proliferation, metastasis, and immune response, which are known to be critically involved in melanoma biology.

These in-silico approaches are cost-effective, time-efficient, and reduce reliance on extensive laboratory experimentation, making them particularly suitable for preliminary drug target identification and biomarker discovery. Therefore, bioinformatics-based analysis offers a valuable strategy for elucidating the molecular mechanisms of melanoma and supporting the development of improved therapeutic interventions. The present study, a bioinformatics-based in-silico approach was employed to construct and analyse a protein–protein interaction network of melanoma-associated genes, followed by functional enrichment and pathway analyses to identify key genes and biological processes involved in melanoma progression.

Methodology

Types of study

The present study is an in- silico (computer- grounded), exploratory and logical bioinformatics study carried out using secondary data. No laboratory trials were performed. Intimately available databases and online bioinformatics tools were used to dissect melanoma- associated genes and understand their functional places in disease development and progression.

1. Identification of melanoma- associated genes using DisGeNE

About DisGeNET

DisGeNET is a comprehensive database that provides information on gene – disease associations collected from curated databases, genome-wide association studies (GWAS), beast models, and published scientific literature.

Working principle

DisGenet links conditions to conditions grounded on experimental substantiation and literature reports. Each gene disease association is supported by substantiation scores indicating the strength of the association.

How DisGeNET was used in this study

The term “Melanoma” was searched in the DisGeNET database. From the recaptured results, melanoma-associated genes were named grounded on their applicability and strong association scores. A final list of 30 melanoma- related genes was attained for farther analysis.

Purpose

To identify genes that are explosively associated with melanoma and are biologically applicable for downstream bioinformatics analysis.

2. Protein – Protein Interaction (PPI) network construction using STRING

About STRING

STRING (Search Tool for the Retrieval of Interacting Genes Proteins) is an online database that predicts relations between proteins.

Working principle

STRING integrates multiple sources of information, including

- Experimental data
- Computational prognostications
- Co-expression patterns
- Pathway databases
- Literature mining

Each commerce is assigned a confidence score.

How STRING was used in this study

The list of melanoma associated genes attained from DisGeNET was uploaded to STRING. Both direct(physical) and circular (function-al) relations were included to induce a protein – protein commerce network.

Purpose

To understand how melanoma- associated proteins interact with each other and to identify important commerce patterns involved in melanoma progression

3. Gene interaction and network expansion using GeneMANIA

About GeneMANIA

GeneMANIA is a bioinformatics tool used to predict gene – gene relations and identify functionally related genes.

Working principle

GeneMANIA uses multiple natural datasets, including

- Co-expression data
- Physical relations
- Pathway information
- inheritable relations
- Co-localization

It also predicts fresh genes that are functionally related to the input gene list.

How GeneMANIA was used in this study

The melanoma- associated gene list was submitted to GeneMANIA to induce a gene commerce network and to identify genes that show strong functional associations with the input genes.

Purpose

To expand the gene network and bet-ter understand the functional connections and natural connectivity among melanoma- related genes

4. Functional and pathway enrichment analysis using Enrichr

About Enrichr

Enrichr is a web- grounded tool used for functional enrichment analysis of gene lists.

Working principle

Enrichr compares the input gene list against multiple natural databases to identify over represented natural functions and pathways.

How Enrichr was used in this study

The melanoma gene list was anatomized using Enrichr to perform

Gene Ontology (GO) natural Process analysis

Pathway enrichment analysis using databases similar as KEGG, Reactome, WikiPath-ways, and BioCarta

Purpose

To identify significantly fortified natural processes and signal-ing pathways involved in melanoma development, progression, metastasis, and immune response.

Results

1. Identification of melanoma- associated genes using DisGeNET

DisGeNET database was used to identify genes significantly associated with melanoma. A hunt for the disease term "Melanoma" recaptured a comprehensive list of genes curated from scientific literature, genome-wide association studies (GWAS), and validated natural databases.

From the recaptured dataset, genes were filtered grounded on their applicability, natural significance, and strength of association with melanoma. After careful webbing, a final set of 30 melanoma- associated genes was named for farther downstream bioinformatics analysis.

Table 1: List of melanoma-associated genes identified using DisGeNET

Gene Symbol	Gene Description	Num Diseases Associated to Gene	Num Variants Associated to Gene	Score
BRAF	B-Raf proto-oncogene, serine/threonine kinase	119	533	1
MITF	melanocyte inducing transcription factor	38	364	1
MC1R	melanocortin 1 receptor	23	308	1
NRAS	NRAS proto-oncogene, GTPase	61	143	1
TP53	tumor protein p53	244	1692	1
TYR	tyrosinase	45	251	1
PTEN	phosphatase and tensin homolog	163	1831	1
CDKN2A	cyclin dependent kinase inhibitor 2A	112	627	1
PARP1	poly(ADP-ribose) polymerase 1	57	8	1
CTLA4	cytotoxic T-lymphocyte associated protein 4	84	135	1
PRAME	PRAME nuclear receptor transcriptional regulator	12	0	1

BRCA2	BRCA2 DNA repair associated	91	10501	1
TERT	telomerase reverse transcriptase	100	1356	1
NFKB1	nuclear factor kappa B subunit 1	29	84	1
IL2	interleukin 2	85	5	0.95
TNF	tumor necrosis factor	312	9	0.95
CD274	CD274 molecule	14	0	0.95
PDCD1	programmed cell death 1	11	1	0.95
POMC	proopiomelanocortin	116	44	0.95
MAP2K1	mitogen-activated protein kinase kinase 1	38	191	0.95
MLANA	melan-A	7	1	0.95
PMEL	premelanosome protein	1	0	0.95
TLR4	toll like receptor 4	95	9	0.95
IFNG	interferon gamma	132	19	0.95
MAPK1	mitogen-activated protein kinase 1	62	17	0.95
SLC45A2	solute carrier family 45member 2	13	140	0.9
GNAQ	G protein subunit alpha q	19	19	0.9
CHEK2	checkpoint kinase 2	64	1991	0.9
MTAP	methylthioadenosine phosphorylase	6	84	0.9
HRAS	HRas proto-oncogene, GTPase	87	246	0.9

The linked genes included crucial oncogenes, tumor suppressor genes, immune non-supervisory genes, and melanocyte-specific labels. Prominent genes similar as BRAF, NRAS, TP53, PTEN, CDKN2A, MAPK1, MAP2K1, MITF, TYR, CTLA4, PDCD1, and CD274 showed strong associations with melanoma, pressing their established places in melanoma initiation, progression, and immune evasion.

These genes are known to be involved in critical natural processes similar as cell proliferation, MAPK signaling, apoptosis regulation, DNA form, melanogenesis, and immune checkpoint regulation. The selection of these genes handed a biologically applicable and well- supported gene set for posterior protein – protein commerce analysis, network expansion, and functional enrichment studies.

Overall, DisGeNET analysis successfully enabled the identification of a curated and disease-applicable gene list, forming the foundation for understanding the molecular mechanisms underpinning melanoma through network-grounded bioinformatics approaches.

2. Protein–Protein Interaction (PPI) network analysis using STRING

The protein–protein interaction (PPI) network of the selected 30 melanoma-associated genes was constructed using the STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) database to explore the functional relationships among the encoded proteins.

The generated STRING network revealed a highly interconnected interaction map, indicating strong functional and biological associations among melanoma-related proteins. The network consisted of 30 nodes, representing individual proteins, connected by multiple edges corresponding to various types of interactions.

STRING analysis integrated different sources of evidence, including experimentally validated interactions, predicted interactions, co-expression data, pathway associations, and literature-derived evidence. Among these, physical and predicted interactions contributed the majority of the connections, suggesting strong experimental and computational support for the observed protein interactions.

Several key hub proteins displayed a high degree of connectivity within the network. Notably, BRAF, NRAS, MAPK1, MAP2K1, KRAS, and HRAS formed a central interaction cluster associated with the MAPK signaling pathway, highlighting its dominant role in melanoma progression. Tumor suppressor proteins such as TP53, PTEN, and CDKN2A were also well connected, indicating their regulatory influence on cell cycle control and apoptosis.

Additionally, proteins involved in melanocyte differentiation and pigmentation (MITF, TYR, PMEL, MLANA) and immune regulation (CTLA4, PDCD1, CD274, IFNG, IL2) showed meaningful interactions, reflecting the multifactorial nature of melanoma involving oncogenic signaling, melanocyte biology, and immune evasion mechanisms.

Overall, STRING-based PPI analysis demonstrated that melanoma-associated proteins are functionally interconnected and participate in coordinated biological pathways. This network provided a strong foundation for subsequent gene interaction expansion and functional enrichment analyses.

Table 2: Functional enrichment themes identified from STRING analysis of melanoma-associated genes

Biological Theme	**Representative GO Biological Process Terms**
Cell proliferation & senescence	Regulation of cell proliferation; cellular senescence
MAPK / ERK signaling	MAPK cascade; ERK1 and ERK2 cascade
Apoptosis	Regulation of apoptotic process; intrinsic apoptotic signaling
Metastasis	Cell migration; regulation of cell adhesion
Immune response	Immune system process; T cell activation

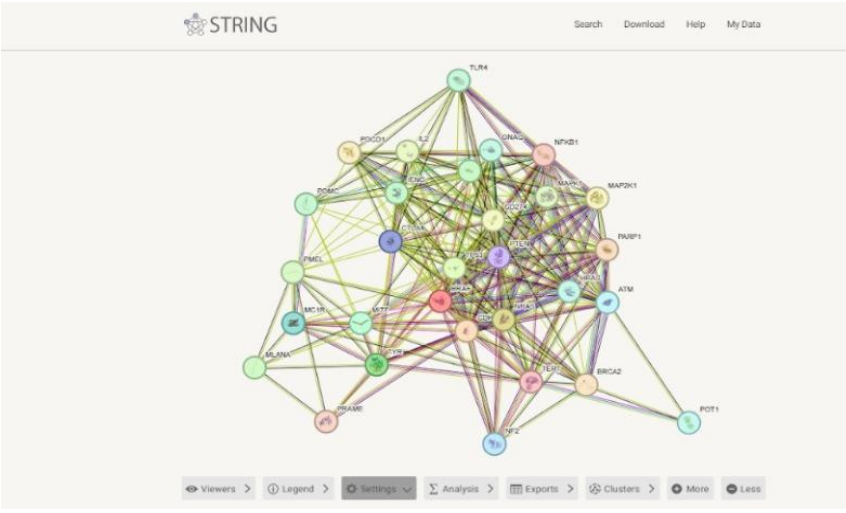

Figure 1: Protein–protein interaction (PPI) network of melanoma-associated genes constructed using STRING database

3. Gene – Gene interaction network analysis using GeneMANIA

To further explore functional relationships among melanoma-associated genes, GeneMANIA was used to construct a gene–gene interaction network based on the previously identified 30 melanoma-related genes.

The GeneMANIA network revealed a high degree of functional connectivity among the input genes, supported by multiple types of biological evidence. The interactions were primarily based on co-expression, physical interactions, pathway co-membership, genetic interactions, and co-localization, indicating that the genes are involved in shared biological functions and regulatory mechanisms.

The analysis demonstrated that genes involved in MAPK signaling (BRAF, NRAS, MAPK1, MAP2K1, HRAS) formed a closely connected cluster, confirming their central role in melanoma oncogenesis. Genes related to melanocyte differentiation and pigmentation (MITF, TYR, MLANA, PMEL) also showed strong co-expression patterns, reflecting their coordinated regulation in melanoma cells.

In addition, immune-related genes such as CTLA4, PDCD1, CD274, IFNG, and IL2 exhibited functional associations, highlighting the involvement of immune regulatory mechanisms and tumor immune interactions in melanoma progression. Tumor suppressor genes including TP53, PTEN, CDKN2A, and BRCA2 were integrated within the network, suggesting their regulatory influence on cell cycle control, DNA repair, and apoptosis.

Overall, GeneMANIA analysis expanded the understanding of the melanoma gene network by illustrating functional relationships beyond direct protein interactions. The results indicate that melanoma-associated genes operate within a tightly connected functional framework, supporting their collective role in disease development and progression. This gene–gene interaction network complemented the STRING-based protein interaction analysis and strengthened the biological relevance of the selected gene set.

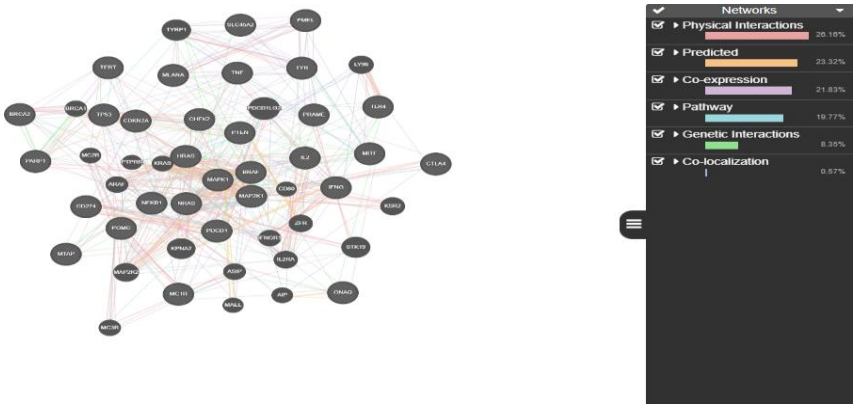

Figure 2: Gene–gene interaction network of melanoma-associated genes generated using GeneMANIA

4. Functional and pathway enrichment analysis using Enrichr

Comprehensive functional and pathway enrichment analysis using Enrichr demon-strated that the selected melanoma-associated genes are extensively involved in multiple biological processes and signaling pathways critical to melanoma initiation, progression, and immune modulation. Gene Ontology enrichment revealed significant over-representation of processes related to cell proliferation and senescence, indicating dysregulated growth control, along with strong enrichment of MAPK/ERK and stress-activated signaling pathways, which are central drivers of melanoma oncogenesis. Pathways involved in apoptosis and intrinsic cell death signaling were also enriched, suggesting mechanisms that promote tumor cell survival and resistance to therapy. In addition, enrichment of processes related to cell migration, adhesion, and extracellular matrix interaction highlights the

molecular basis of melanoma invasiveness and metastatic spread. Immune-related processes, including immune system regulation, T-cell activation, and interferon-gamma pro-duction, further emphasize the importance of tumor immune interactions and immune evasion mechanisms in melanoma biology.

Pathway enrichment across multiple databases, including KEGG (2021), Reactome (2024), WikiPathways (2024), BioCarta (2016), and Panther (2016) (4-8), consistently identified key melanoma-relevant pathways such as MAPK signaling, melanogenesis, cell cycle control, DNA repair mechanisms, and immune checkpoint signaling. The final comparative pathway table summarizing gene counts across these databases revealed that core oncogenic genes such as MAPK1, HRAS, BRAF, NRAS, and MAP2K1 were enriched across the highest number of path-way resources, indicating their central and conserved roles in melanoma signaling networks. Similarly, immune regulatory genes including IL2, IFNG, CTLA4, and PDCD1 were represented in multiple databases, reflecting their broad involvement in immune response and immunotherapeutic relevance. Genes associated with melanocyte biology and pigmentation showed more pathway-specific enrichment, supporting their specialized functional roles. Overall, the pathway count analysis confirms that melanoma progression is driven by a combination of widely con-served oncogenic signaling pathways and specialized biological processes, rein-forcing the robustness and biological significance of the Enrichr enrichment results.

Table 3: Pathway enrichment across databases (with gene counts)

Gene	KEGG 2021	Reactome Pathways 2024	Wiki Pathways 2024	Biocarta 2016	Panther 2016	Total
BRAF	YES	YES	YES	NO	YES	4
MITF	YES	NO	YES	YES	NO	3
NRAS	YES	YES	YES	NO	YES	4
PTEN	YES	NO	YES	NO	YES	3
NFKB1	YES	NO	YES	NO	YES	3
IL2	YES	YES	YES	NO	YES	4
TNF	YES	NO	YES	YES	NO	3
MAP2K1	NO	YES	YES	YES	YES	4
IFNG	YES	YES	YES	NO	NO	3
MAPK1	YES	YES	YES	YES	YES	5
GNAQ	YES	NO	YES	YES	YES	4
HRAS	YES	YES	YES	YES	YES	5

5. Pathway analysis using Reactome

Reactome pathway analysis was performed to obtain a comprehensive overview of the biological pathways associated with the melanoma-related gene set. Mapping of the selected genes onto the Reactome database revealed their involvement across multiple core cellular and disease-related pathways, highlighting the complex and multifactorial nature of melanoma.

The Reactome overview indicated significant enrichment of genes within signal transduction pathways, particularly those involved in oncogenic signaling cascades, which are central to melanoma development and progression. Prominent enrichment was also observed in cell cycle regulation and programmed cell death, reflecting dysregulated cell proliferation and altered apoptotic mechanisms characteristic of melanoma cells.

Pathways related to DNA replication and DNA repair were represented, suggesting the involvement of genomic instability and impaired DNA dam-age response in melanoma progression.

In addition, Reactome analysis highlighted the participation of melanoma-associated genes in immune system–related pathways, supporting the role of immune regulation and tumor immune interactions in melanoma biology. Enrichment of pathways associated with gene expression and transcription, chromatin organization, and metabolism of proteins further indicated widespread alterations in fundamental cellular processes. Pathways related to extracellular matrix organization, cell–cell communication, and vesicle-mediated transport were also represented, emphasizing mechanisms contributing to tumor invasion and metastasis.

Overall, Reactome pathway analysis provided a global functional context for the melanoma gene set, demonstrating that these genes are distributed across major bio-logical systems involved in oncogenic signaling, immune response, cell cycle control, apoptosis, and cellular organization. These findings complement the results obtained from Enrichr and network analyses, reinforcing the biological relevance of the identified pathways in melanoma progression.

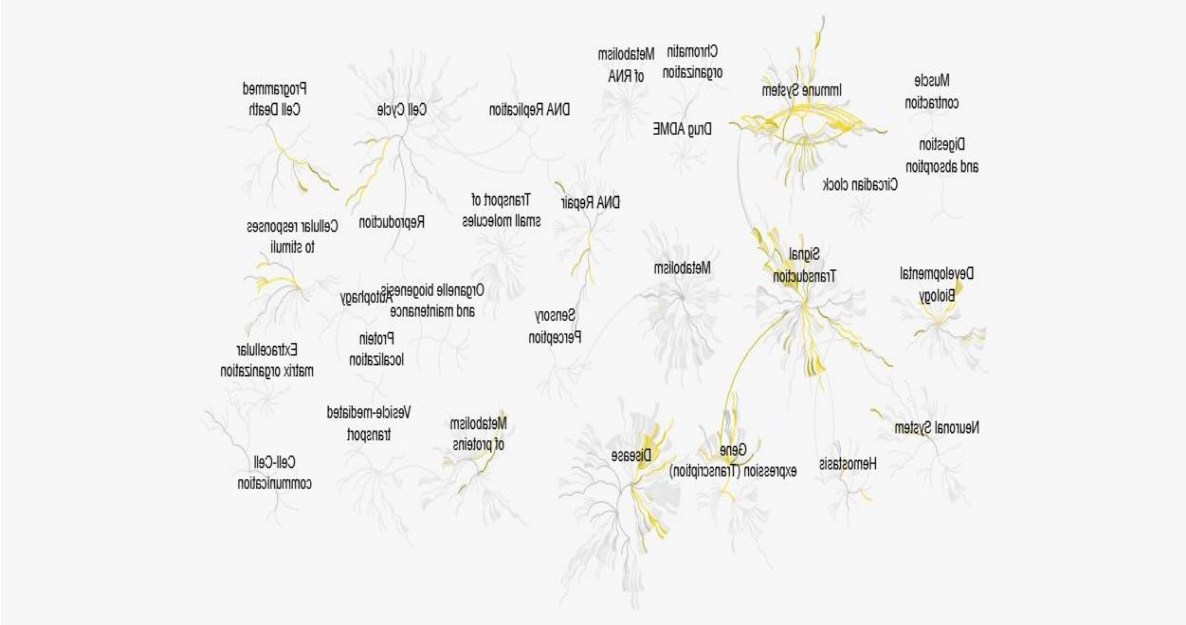

Figure 3: Reactome pathway overview highlighting major biological pathways enriched by melanoma-associated genes

Discussion

The present bioinformatics study explored the molecular mechanisms underlying melanoma by integrating gene–disease association analysis, interaction network construction, and functional and pathway enrichment analysis. Melanoma-associated genes identified through DisGeNET, including BRAF, NRAS, TP53, PTEN, and CDKN2A, provided a biologically relevant set for downstream analysis, reflecting key roles in cell proliferation, apoptosis, and genomic stability (9). Protein–protein interaction analysis using STRING revealed highly interconnected networks, particularly around MAPK signaling, highlighting its central role in melanoma progression (10). GeneMANIA further demonstrated functional associations involving melanocyte differentiation, DNA repair, and immune regulation, emphasizing the coordinated activity of multiple biological systems, including immune

evasion mechanisms (11). Functional enrichment via Enrichr and Reactome confirmed the involvement of processes such as MAPK/ERK signaling, apoptosis, cell migration, DNA repair, and immune checkpoint pathways, reflecting both aggressive tumor behavior and specialized melanocyte biology (12). Overall, the integration of multiple bioinformatics tools provided complementary insights into gene interactions and pathways, identifying potential biomarkers and therapeutic targets, though experimental validation is needed to confirm these in-silico predictions.

Conclusion

The present study successfully employed a network-based bioinformatics approach to investigate the molecular mechanisms underlying melanoma by integrating gene–disease association analysis, interaction network construction, and functional and pathway enrichment analysis. Using DisGeNET, a curated set of 30 melanoma-associated genes was identified, providing a biologically relevant foundation for downstream analysis. Protein–protein interaction analysis using STRING and gene–gene interaction analysis using GeneMANIA revealed a highly interconnected network, indicating coordinated regulation among genes involved in melanoma development and progression.

Functional and pathway enrichment analyses using Enrichr and Reactome demonstrated that the identified genes are significantly involved in key biological processes, including cell proliferation and senescence, MAPK/ERK signaling, apoptosis regulation, cell migration and metastasis, immune response, DNA repair, and melanogenesis. The consistent enrichment of the MAPK signaling pathway across multiple databases highlights its central role in melanoma oncogenesis. Furthermore, the involvement of immune regulatory pathways and immune checkpoint genes such as CTLA4, PDCD1, and CD274 underscores the importance of tumor–immune interactions and supports the clinical relevance of immunotherapy in melanoma treatment.

Key hub genes, including BRAF, NRAS, MAPK1, MAP2K1, TP53, CDKN2A, MITF, and HRAS, were identified as major contributors linking multiple pathways, making them potential biomarkers and therapeutic targets. The comparative pathway analysis across different databases further confirmed that melanoma progression is driven by both conserved oncogenic signaling pathways and specialized biological processes related to melanocyte function.

Overall, this study demonstrates the effectiveness of bioinformatics and systems biology approaches in clearly elucidating complex disease mechanisms such as melanoma. The findings provide valuable insights into the molecular framework of melanoma and highlight the utility of in-silico analysis as a cost-effective and efficient strategy for identifying critical genes and pathways that may aid future experimental research and drug discovery efforts.

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