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Pharmacogenetics of BRAF in melanoma: mechanisms of drug resistance and therapeutic optimization – a systematic review

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Abstract

Background: Melanoma is the most lethal form of skin cancer with the highest mortality rate.

Objective: To review research directions in pharmacogenetics related to the *BRAF* gene in melanoma.

Methods: Data were extracted from three databases (PubMed, The Cochrane Library, and Science Direct) for studies published between January 2017 and December 2024, focusing on pharmacogenetics and the role of the *BRAF* gene in melanoma treatment.

Results: Three main research directions were identified: (1) Elucidating mechanisms of drug resistance in BRAF-mutant patients, including NRAS/MEK mutations, PTEN loss, and drug transporter gene variants; (2) Utilizing genetic biomarkers (e.g., PD-L1) and combining targeted therapy with immunotherapy to enhance treatment efficacy; (3) Applying next-generation sequencing (NGS) for mutation detection and treatment regimen personalization.

Conclusion: Clarifying drug resistance mechanisms, optimizing combination therapies, and integrating genetic technologies will contribute to improved treatment outcomes for BRAF-mutant melanoma.

Keywords: Pharmacogenetics, polymorphism, BRAF gene, melanoma, systematic review

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1. INTRODUCTION

Melanoma is a malignant tumor of melanocytes, recognized as the most invasive and aggressive form of skin cancer. The 5-year survival rate drops below 5% once metastasis occurs [1]. Current primary treatment modalities include surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, and combination therapies [2]. In recent years, pharmacogenetics has emerged as a prominent field, significantly contributing to the advancement of personalized medicine. Instead of using drugs at standard doses, patients receive personalized dosing regimens based on genetic testing results [3]. Furthermore, genetic biomarkers play an essential role in selecting appropriate therapies and improving immune response through targeted and immunotherapeutic strategies. The application of genetic analytical tools not only aids in optimizing treatment but also helps predict patient responses to novel therapies [4]. In this context, this systematic review aims to synthesize current evidence and elucidate key research directions in the pharmacogenetics of the *BRAF* gene, which encodes the B-Raf protein, in melanoma.

2. MATERIALS AND METHODS

2.1. Objectives

This study was designed as a systematic review of literature published in the last 8 years (2017 - 2024) concerning the pharmacogenetics of the *BRAF* gene in cutaneous melanoma.

2.2. Methods

Data were extracted and searched from three databases PubMed, The Cochrane Library, and Science Direct, for relevant studies related to the pharmacogenetics and impact of the *BRAF* gene in melanoma treatment, following PRISMA 2020 guidelines [5]. The search strategy was constructed using the PICO framework to define keywords. Synonyms for the keywords (title) were identified and combined using Boolean operators (AND, OR) to optimize the search.

Table 1. Keywords for the PICO model

Criteria	Description	Keywords
Population (P)	Patients with BRAF-mutant melanoma	Melanoma; *BRAF*
Intervention (I)	Treatment with targeted therapy	Targeted therapy; BRAF inhibitors (vemurafenib, dabrafenib); MEK inhibitors (trametinib, cobimetinib)
Comparison (C)	Comparison with other therapies: surgery, radiotherapy, chemotherapy, immunotherapy	No
Outcome (O)	Polymorphism; Genetic factors; Influencing genes	Polymorphism; Pharmacogenomic; Gene

Table 2. Research search strategy across databases

Database	Search Strategy	Filters
Pubmed	((“melanoma” OR “skin cancer”) AND (“BRAF” OR “V600E” OR “V600K” OR “targeted therapy” OR “BRAF inhibitors” OR “vemurafenib” OR “dabrafenib” OR “MEK inhibitors” OR “trametinib” OR “cobimetinib”)) AND (“pharmacogenomic” OR “GENE” OR “polymorphism”)	- Publication date: 2017-2024 - Language: English or Vietnamese - Text availability: Free full text. - Article type: Randomized controlled trials (RCTs), observational studies.
Cochrane	#1: Melanoma OR metastatic melanoma OR melanoma patient OR advanced melanoma #2: Serine/threonine protein kinase B-raf OR BRAF inhibitors OR Vemurafenib OR Dabrafenib OR Encorafenib OR mitogen-activated protein kinase OR MEK inhibitors OR Trametinib OR Cobimetinib OR Binimetinib OR BRAF/MEK inhibitors OR BRAF	- Publication date: 2017-2024. - Publication Type: Journals. - Access Status: Open access content. - Language: English or Vietnamese (Use “Languages” filter to select these languages).

	mutation OR Targeted Therapy OR precision medicine #3: Polymorphism OR Pharmacogenomic OR Pharmacogenetic marker OR gene Search: #1 AND #2 AND #3	
Science Direct	("Melanoma") AND ("BRAF/MEK inhibitors" OR "Targeted Therapy") AND ("polymorphism") AND ("GENE" OR "Genetic" OR "Pharmacogenomic" OR "drug metabolism")	- Publication date: 2017-2024. - Article type: Research articles. - Language: English. - Access type: Open access & open archive.

2.2.1. Inclusion criteria

- Patients with melanoma harboring *BRAF* gene mutations;
- Evaluation of targeted therapy outcomes;
- Comparison with other treatment modalities: surgery, radiotherapy, chemotherapy, immunotherapy;
- Measured outcomes include: genetic polymorphisms; pharmacogenetic factors (drug resistance mechanisms, toxicity, adverse effects); influential genes;
- Study designs: observational studies or randomized controlled trials.

2.2.2. Exclusion criteria

- Studies not related to melanoma;
- Studies lacking treatment outcome assessment or mechanism of action evaluation;
- Non-full-text publications;
- Systematic reviews, meta-analyses, case reports, letters to editors;
- Studies published in languages other than Vietnamese and English.

2.3. The process of screening titles and abstracts

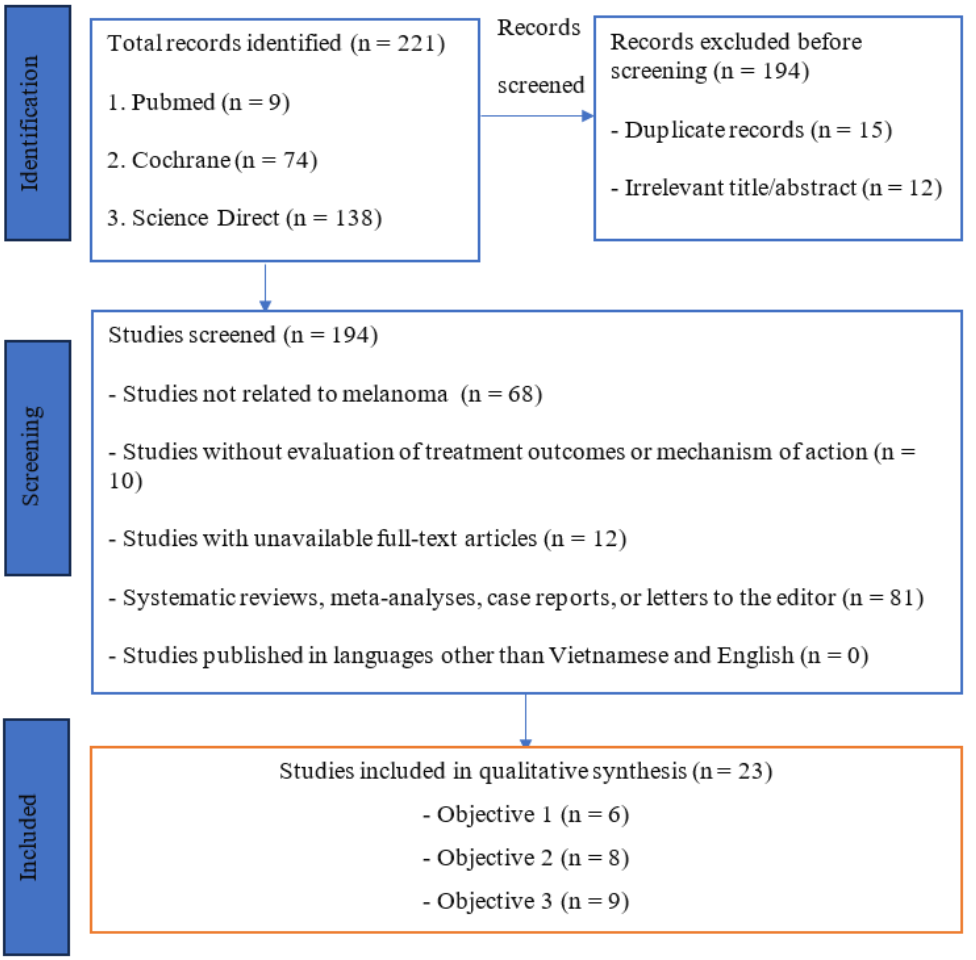
The titles and abstracts of the search publications were independently screened by members N.H.T.V and N.N.B.N to select the relevant studies. Any discrepancies between the researchers were resolved through discussion and consensus with the third member (L.N.L). N.H.T contributed to manuscript preparation.

2.4. Data analysis, statistical and study quality assessment

The search, screening, and study selection process were managed using EndNote X9 and Rayyan software. Data synthesis and analysis were subsequently processed using Microsoft Excel 365. Study quality was assessed using the Newcastle-Ottawa Scale for observational research and the cochrane risk of bias tool for clinical trials.

3. RESULTS

A total of 221 studies were excluded during the screening process. After full-text analysis, 23 studies were selected for final inclusion (Flowchart 1).



Flowchart 1. Flowchart of study search and selection results

The characteristics of the included studies are summarized in Table 3 bellow:

Table 3. Characteristics of the selected studies

Author, country, year	Objectives	Research methodology & sample size	Gene sequencing method
Nelson *et al.*, USA, (2024) [6]	Investigate the efficacy of RAF inhibitors (RAFi) in patients with BRAF-mutant solid tumors.	Observational study of 44 patients with tumors harboring RAF mutations.	NGS
Gassenmaier M. *et al.*, Germany & Switzerland, (2020) [7]	Analyze DNA methyltransferase 1 (Dnmt1) expression in melanocytic tumors and determine its relationship with cell proliferation and response to B-Raf and MEK inhibitors. Explore Dnmt1's potential as a	Observational study; immunohistochemistry and fluorescence analysis to measure Dnmt1 and Ki-67 expression in tumor tissues; melanoma cell line cultures treated with	Gene expression data from gene expression omnibus (GEO) and single-cell RNA expression analysis of

Author, country, year	Objectives	Research methodology & sample size	Gene sequencing method
	target for combined epigenetic and immunotherapy.	B-Raf (vemurafenib) and MEK (cobimetinib) inhibitors to monitor Dnmt1 expression changes; western blot for protein levels; public dataset gene expression analysis; statistical analysis using SPSS and Prism. Includes 83 tumors and 12 cutaneous melanoma cell lines.	subcutaneous xenograft models.
Kadioglu O. *et al*., Germany & Portugal, (2020) [8]	Analyze the role of mutations and expression levels of ABC (ATP-binding cassette) transporter proteins in multi-drug resistance (MDR) and patient survival. Specifically, identify links between mutations/expression and drug resistance/prognosis to propose new treatment strategies.	Observational study; RNA sequencing to identify mutations in ABC transporter proteins in 19 cancer patients; analysis of mutation and gene expression data from the cBioPortal database (>11,000 patients across 23 cancer types); homology modeling and molecular docking analysis to assess mutation impact on structure and drug interaction; Kaplan-Meier survival analysis; and statistical analysis using SPSS with the log-rank test.	RNA sequencing to identify mutations in genes encoding ABC transporter proteins in 19 patients. Analysis of RNA-seq data and mapping of mutations (missense, nonsense) on coding regions.
Mourad A.M. Aboul-Soud *et al*., Saudi Arabia, (2021) [9]	Detect mutations likely to affect cancer treatment outcomes, including drug efficacy and toxicity, to support personalized therapy.	Observational study; DNA collected from peripheral blood of 181 patients with solid tumors; whole exome Sequencing (WES) using sureselectXT human all exon V6 + UTR kit and Illumina NextSeq 550 (average 100× coverage); WES data analysis using GATK; variant assessment with ANNOVAR, PolyPhen, SIFT, and	WES

Author, country, year	Objectives	Research methodology & sample size	Gene sequencing method
		CADD; comparison with PharmGKB database for drug-response variants.	
Wang *et al*., USA, (2019) [10]	Investigate drug resistance mechanisms when using dual MAPK pathway inhibition (BRAF and MEK inhibitors) in tumors harboring BRAF V600E mutations.	Observational study using drug-resistant cell lines with BRAF-V600E mutations and patient-derived xenograft (PDX) mouse models to evaluate resistance mechanisms.	RNA-seq; FGFR protein quantification via western blot.
Cheng *et al*., USA, (2019) [11]	Develop and clinically validate a 28-gene cfDNA panel to analyze common mutations in solid cancers. Evaluate the panel's effectiveness in detecting pathogenic mutations, monitoring disease progression, and identifying resistance mechanisms.	Observational study; 163 blood samples collected from 123 stage IV cancer patients (including 14 melanoma cases) to isolate cell-free DNA (cfDNA).	NGS; mutations filtered by allele frequency (>0.25%) and common variants removed based on databases (e.g., ExAC).
Liu *et al*., USA, (2024) [12]	Gene grouping to optimize personalized treatment and prognosis for patients with Colorectal Melanoma (CRM).	Prospective observational study of 46 CRM patients over 16 years; categorized into Immune Depletion group (C1) and DNA Repair group (C2).	Multi-omic analysis (proteomics and genomics); Support Vector Machine (SVM) machine learning algorithm to classify patients based on protein expression.
Gao *et al*., USA, (2018) [13]	Analyze gene fusion events across 33 cancer types, identifying their role in oncogenesis and potential for targeted therapy. Evaluate gene expression, kinase fusion structures, and the feasibility of targeted or immunotherapy based on gene fusions.	Observational study; analysis of 9,624 cancer samples and 713 normal samples from The Cancer Genome Atlas (TCGA) project.	RNA-seq, WGS
Bielski *et al*., USA, (2018) [14]	Analyze the allelic imbalance of driver mutations in oncogenes, specifically focusing on BRAF-	Observational study of 13,448 cancer samples across 53 cancer types,	NGS

Author, country, year	Objectives	Research methodology & sample size	Gene sequencing method
	related mutations, to determine their impact on cancer progression and response to targeted therapy.	including cutaneous melanoma samples.	
Rouillé *et al*., France, (2019) [15]	Determine the efficacy of MEK and Akt inhibitors in reducing cell proliferation and viability in NRAS-mutant lCMN cells. Build preclinical models to test the effectiveness of local targeted treatment for lCMN.	Clinical trial of 17 patients.	Pyrosequencing and E-ice-COLD-PCR
Gupta *et al*., United Kingdom, (2020) [16]	Predict biomarkers for the response of BRAF-wildtype melanoma to MEK inhibitors to improve treatment selection. Specifically, evaluate the roles of DUSP4 and ETV4 as biomarkers and regulators of MEK inhibitor sensitivity.	Clinical trial involving 64 patients from the DOC-MEK trial, using data from 59 genetic sequencing samples.	NGS
Atkins *et al*., USA, (2022) [17]	This Phase III study aims to determine the optimal treatment sequence between immune checkpoint therapy (nivolumab /ipilimumab) and molecular targeted therapy (dabrafenib/ trametinib) for untreated BRAF V600-mutant metastatic melanoma patients. Primary objective: 2-year survival rate.	Clinical trial of 265 BRAF-V600 mutant metastatic melanoma patients, randomized to receive nivolumab/ ipilimumab (A) or dabrafenib/trametinib (B) in Step 1. upon progression, patients crossed over to Step 2 to receive the alternative therapy (Group C or D).	Study does not mention the use of gene sequencing.
Robert *et al*., multi-national, (2022) [18]	Analyze predictive biomarkers for treatment benefit from atezolizumab combined with vemurafenib and cobimetinib in BRAF V600-positive melanoma patients.	Clinical trial of 514 patients randomized into the atezolizumab group (n=256) or control group (n=258).	NGS; RNA sequencing used to analyze the IFN-γ gene signature.
Dummer *et al*., multi-national, (2022) [19]	Evaluate the efficacy and safety of spartalizumab combined with dabrafenib and trametinib (sparta-DabTram) versus placebo with dabrafenib and trametinib	Clinical trial of 532 randomized patients: 267 in the sparta-DabTram group and 265 in the placebo-DabTram group.	No specific mention of the gene sequencing method used to determine TMB

Author, country, year	Objectives	Research methodology & sample size	Gene sequencing method
	(placebo-DabTram) in patients with unresectable or metastatic BRAF-V600 mutant melanoma.		status.
Moranova *et al*., USA, (2024) [20]	Improve targeted therapy efficacy while providing data on gene expression levels and treatment response in cancer cells.	Observational study; integrated genetic and pharmacological data from 51 melanoma patients.	Multi-omic tools and CRISPR/Cas9
Pallocca *et al*., Italy (2024) [21]	Validate genetic biomarkers for immunotherapy and targeted therapy.	Retrospective multicenter observational study of 82 stage III-IV melanoma patients.	NGS
Rosenthal *et al*., USA, (2017) [22]	Evaluate the clinical efficacy of a 25 gene pan cancer panel (including melanoma related genes) to identify hereditary cancer risk. Compare the gene panel test with targeted testing.	Observational study; 252,223 cases; DNA extracted from blood or saliva; gene sequencing performed using Illumina HiSeq2500/MiSeq technology. Evaluation of pathogenic variants (PVs) and variants of unknown significance (VUS) according to ACMG standards.	NGS and microarray CGH to confirm structural variants.
Shaughnessy *et al*., USA, (2020) [23]	Classify melanoma based on TERT promoter mutation status. Focus on the relationship between TERT promoter mutations, TERT expression levels, telomerase activity, and telomere length. Develop a classification system to explain the impact of these mutations.	Observational study; identified mutations in 60 cutaneous melanoma cell lines (58/60 or 96.7% carried TERT promoter mutations); qPCR to analyze gene expression and telomere length; statistical analysis via linear regression. Cell lines were validated for integrity and cultured in standard media.	Sanger sequencing
Garg *et al*., Canada, (2020) [24]	Evaluate the diagnostic efficacy of Next-Generation Sequencing (NGS) via the TruSight Tumor 26 (TST26) panel in analyzing melanoma, colorectal cancer (CRC), and gastrointestinal	Observational study; DNA extracted from FFPE samples and sequenced using TST26 (Illumina). Data analysis used NextGENe, MiSeq reporter,	Illumina MiSeq system with TST26 panel, Sanger sequencing.

Author, country, year	Objectives	Research methodology & sample size	Gene sequencing method
	stromal tumors (GIST). Compare NGS variant detection with non-NGS methods.	and variant studio software. NGS-detected variants were validated by sanger sequencing and mutation -specific PCR.	
Li *et al*., China, (2021) [25]	Identify differentially expressed immune-related genes in melanoma, build a risk model based on key immune genes, and evaluate the link between immune signatures and immune cell distribution in the tumor environment.	Observational study; analysis of transcriptomic data from public databases and statistical analysis to identify differentially expressed immune genes, build a risk model, and evaluate links with clinical factors.	Pre-existing transcriptomes from TCGA and GTEx.
Hodi *et al*., USA, (2021) [26]	Investigate the link between tumor mutational burden (TMB), inflammatory gene expression signatures, and BRAF mutations with tumor response, progression-free survival (PFS), and overall survival (OS) in advanced melanoma patients treated with immunotherapy. Uses data from phase III checkMate 066 and 067 trials.	Observational study; Cox regression analysis used to assess links between biomarkers and clinical outcomes. Kaplan-Meier curves used to illustrate differences in PFS and OS.	WES, agilent sureSelectXT v5, illumina hiSeq2500, truSeq RNA access (Illumina).
Zhan *et al*., China, (2023) [27]	Expand personalized treatment options for cancer patients by combining NGS and proteomics (genoproteomics), focusing on identifying driver mutations and protein overexpression for targeted therapies.	Observational study; samples analyzed using both NGS (cancer-specific panels) and label-free LC-MS/MS proteomics on 169 clinical specimens.	NGS
Li *et al*., China, (2022) [28]	Provide a comprehensive description of the genetic characteristics of primary malignant melanoma of the esophagus (PMME), a rare cancer with a poor prognosis.	Observational study; whole exome sequencing performed on FFPE samples, followed by analysis of gene mutations, copy number variations (CNV), mutational signatures, and intratumoral heterogeneity (ITH) across 47 specimens.	WES, Geneplus -2000, Illumina HiSeq X10.

3.1. Quality assessment of included studies

Observational Studies: The quality of the observational studies was assessed using the Newcastle-Ottawa scale (NOS). Out of the 17 observational studies evaluated, 100% were classified as high quality (≥ 7 points). The primary strengths of these high-quality studies lies in the representativeness of the patient samples and the comparability between groups. However, some studies could further improve regarding the "comparability of cases and controls" criterion to achieve higher methodological rigor [10,11,20,26,27]

Clinical trials: The quality assessment of clinical trials using the cochrane risk of bias tool is presented in table 4.

Table 4: Quality assessment of clinical trials using the cochrane risk of bias tool

Nghiên cứu	(a)	(b)	(c)	(d)	(e)	(f)	(g)
Rouillé (2019) [15]	~	~	+	~	-	+	+
Gupta (2020) [16]	+	+	+	~	~	+	+
Atkins (2022) [17]	+	~	+	~	-	+	+
Robert (2022) [18]	~	~	+	~	-	+	+
Dummer (2022) [19]	+	~	+	~	-	+	+

Note: (a) Random sequence generation (selection bias); (b) Allocation concealment (selection bias); (c) Selective reporting (reporting bias due to selective outcome reporting); (d) Other bias; (e) Blinding of participants and personnel; (f) Blinding of outcome assessment; (g) Incomplete outcome data

- = high risk, ~ = unclear risk, + = low risk

3.2. Research direction 1: pharmacogenetic studies identifying and analyzing drug resistance mechanisms in Braf-mutant melanoma

Targeted therapy has significantly improved outcomes for BRAF-mutant melanoma patients using BRAF inhibitors (e.g., vemurafenib, dabrafenib) and MEK inhibitors. However, drug resistance remains a major challenge, preventing long-term responses. A 2024 study by Nelson *et al*. using NGS on 44 melanoma patients identified multiple resistance mechanisms, including alterations in receptor tyrosine kinases (RTKs), NRAS mutations, NF1 loss, and changes in transcriptional regulators. Tumor cells can also develop phenotypic plasticity, switching between cellular states and reducing their dependence on the MAPK pathway, thereby diminishing the efficacy of BRAF/MEK inhibition. Other mutations, such as PTEN loss or cyclin D1 upregulation, further contribute to resistance, underscoring the importance of understanding genetic mechanisms for developing more effective strategies [6]. Gassenmaie *et al*. (2020), using Gene Expression Omnibus (GEO) data and RNA analysis, discovered that Dnmt1 expression strongly correlates with the proliferation marker Ki-67, independent of BRAF status. Dnmt1 expression decreased upon BRAF and MEK inhibition but rebounded with the emergence of resistance [7].

Mourad *et al*. (2021), through whole-

exome sequencing (WES) of 181 patients, linked variants in CYP2D6 (*10, *4) and ABCG2 (rs2231142) to drug metabolism and resistance. The CYP2D6 *10 allele (25% frequency) reduces enzyme activity, affecting the metabolism of various drugs, including cancer therapeutics. The ABCG2 rs2231142 variant was associated with drug resistance, as this transporter pumps chemotherapeutic agents out of cancer cells, impacting treatment efficacy [9]. Kadioglu *et al*. (2020) used gene sequencing to identify nonsense mutations in ABCC1 (Q185*, R1385*) and ABCC5 (Q743*), suggesting a loss of function that may reduce drug efflux [8]. Wang *et al*. (2020) identified Fibroblast Growth Factor 1 (FGF1) as strongly upregulated upon dual BRAF/MEK inhibition. Increased FGF1 expression led to autocrine activation of FGFR, sustaining ERK signaling and reducing therapy efficacy. FGFR inhibition overcame resistance in cell lines and patient-derived xenograft models, enhancing tumor cell death and preventing the outgrowth of resistant cells. Notably, serum FGF1 levels correlated with patient prognosis, highlighting its potential as a personalizing target and immunotherapy. These findings confirm the potential of combining FGFR inhibitors with BRAF/MEK inhibitors to extend treatment response and manage resistance [10]. Cheng *et al*. (2019) also identified secondary mutations in NRAS or MEK that reactivate MAPK signaling, reducing the efficacy of BRAF-targeted therapy. Upregulation of invasion-related genes like FGFR1 was also linked to resistance [11].

3.3. Research direction 2: pharmacogenetics for optimizing targeted and immunotherapy via genetic biomarkers

A prospective observational study by Liu *et al.* (2024) of 46 mucosal melanoma patients over 16 years stratified patients into an immune-deficient subtype (C1) and a DNA repair-proficient subtype (C2) [12]. The C1 subtype, characterized by high expression of immune-related (LILRB4, ITGAX), metabolic (FABP3, CES1), and metastatic (CAPG) proteins, featured an immunosuppressive microenvironment and metabolic dysregulation, with the MYCN/NAGK index predicting poor prognosis. In contrast, the C2 subtype, with better DNA repair and immune function, responded more effectively to immunotherapy, emphasizing the potential for personalized treatment [12]. Supporting this, Gao *et al*. (2018) found that 16.5% of cancers were driven by gene fusions, with a high proportion being targetable kinase fusions involving BRAF [13]. Bielski *et al*. (2018) demonstrated that patients with loss of the wild-type BRAF allele had a longer progression-free survival (PFS) on BRAF inhibitors, with a 60% complete response rate in this group versus 8% in others, establishing BRAF allelic imbalance as a key predictive factor [14]. Furthermore, combined MEK and Akt inhibition reduced cell proliferation and survival, showing efficacy for up to 30 days in xenograft models, suggesting a potential targeted approach for specific melanoma subtypes [15]. Additionally, Gupta *et al*. (2020) showed that high DUSP4 expression was associated with better response to selumetinib. Knocking down DUSP4 increased cell survival and reduced drug sensitivity, confirming its role in mediating response to MEK inhibition [16].

3.4. Research direction 3: pharmacogenetic studies evaluating genomic sequencing for predicting melanoma

Research confirms that modern mutation detection methods are strongly linked to treatment efficacy. Next-

Generation Sequencing (NGS) and digital droplet PCR (ddPCR) were validated as more effective than traditional PCR for distinguishing mutants from wild-type alleles [20]. While studies of SNVs and INDELs showed homogeneity in certain melanoma groups, copy number variation (CNV) patterns were less clear due to technological and sample size limitations. A key finding was the relationship between specific gene mutations and treatment outcomes; mutations in PDGFRB, NOTCH3, and RET were associated with improved overall and progression-free survival, particularly with immune checkpoint inhibitors, whereas NOTCH4 mutations were detrimental [21]. Moreover, the presence of mutations in melanoma-associated genes like CDKN2A and CDK4 in patients without a family history indicates these may be risk factors for sporadic cancer [22]. NGS also improved the detection of genetic variants in melanoma and colorectal cancer (CRC), identifying clinically significant variants in an additional 20% of melanoma cases and in 94% of CRC samples. However, for GIST, NGS did not outperform Sanger sequencing due to limitations in detecting complex variants in KIT exon 11 [24]. Finally, the integration of NGS with proteomics (genoproteomics) expanded treatment options for cancer patients, identifying actionable mutations in 14 genes and 61 drug targets, providing potential treatment avenues for 85% of patients in the study [27].

4. DISCUSSION

This review systematizes three main research directions in the pharmacogenetics of the *BRAF* gene in melanoma. First, studies have elucidated numerous resistance mechanisms in BRAF-mutant patients, particularly MAPK pathway reactivation via secondary NRAS or MEK mutations, RTK alterations, PTEN loss, and variants in drug transporter (ABCG2, ABCC1/5) and metabolism (CYP2D6) genes. These factors significantly contribute to treatment failure, highlighting the role of pharmacogenetics in identifying and managing resistance.

Second, research demonstrates the utility of genetic biomarkers (e.g., FABP3, CES1, CAPG, DUSP4, FGF1) in personalizing targeted and immunotherapy. Combining BRAF and MEK inhibitors, or integrating them with immunotherapy (anti-PD-1, anti-CTLA-4), has been shown to prolong progression-free survival and reduce resistance rates.

Third, the application of NGS is increasingly emphasized for the early detection of prognostically significant mutations and guiding therapy selection. It is a crucial tool for precision medicine, especially in patients with complex genetic profiles. Research confirms that modern mutation detection methods such as NGS and ddPCR are more effective than traditional PCR in distinguishing mutant and wild-type alleles and are strongly linked to treatment outcomes. The combination of NGS with proteomics has expanded treatment options, identifying mutations and drug targets for 85% of patients.

Based on these findings, future research should focus on developing next-generation inhibitors, integrating artificial intelligence (AI) for genetic data analysis, evaluating the impact of the tumor microenvironment, and exploring the efficacy of combining gene therapy with targeted treatments. These directions will not only expand our understanding of cancer biology but also help establish a foundation for more effective personalized treatment in the future.

5. CONCLUSIONS

This systematic review of research directions in the pharmacogenetics of the B-Raf encoding gene reveals significant potential for enhancing treatment efficacy and improving prognosis in melanoma. Continued investigation into resistance mechanisms, therapy optimization, and the application of genomic technologies will be pivotal in shaping future treatment strategies.

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