Systematic druggable genome-wide Mendelian randomization identifies therapeutic targets for basal cell carcinoma

Tianyu E[1], Jintao Yu[2], Chen Bi[3], Benjia Liang[2]*

[1]Shandong First Medical University, Jinan, Shandong, China
[2]Department of Gastrointestinal Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China
[3]Department of Burns and Plastic Surgery, Weihai Central Hospital Affiliated to Qingdao University, Weihai, Shandong, China

Submitted: 23 May 2025; **Accepted:** 5 September 2025
Online publication: 6 November 2025

Arch Med Sci
DOI: https://doi.org/10.5114/aoms/210332

***Corresponding author:**
Benjia Liang PhD
Department of Gastrointestinal Surgery
Shandong Provincial Hospital Affiliated to Shandong First Medical University
Jinan, Shandong
China
E-mail: liangbj127@hotmail.com

Abstract

Introduction: Basal cell carcinoma (BCC) is the most common type of skin cancer, with its incidence increasing annually, posing a significant challenge to public health. Currently, the treatment of BCC mainly includes surgical resection, radiotherapy, and pharmacotherapy. However, for high-risk or recurrent BCC cases, traditional treatments may be limited in efficacy, and there is an urgent need to explore more effective targeted therapeutic strategies. This study aims to identify and validate potential druggable genes for BCC treatment by integrating multi-omics and pharmacogenomics approaches.
Material and methods: Utilizing pharmacogenomics, transcriptomics, proteomics, and genome-wide association study (GWAS) data, we employed Mendelian randomization (MR) and Bayesian colocalization analyses to identify genes associated with BCC development. Phenome-wide Mendelian randomization (Phe-MR) analysis was further conducted to elucidate the causal relationships between these genes and various disease phenotypes.
Results: The study identified PSMB9, TGM3, CTSS, HLA-DQA2, and RNASET2 as potential drug targets, with PSMB9 and RNASET2 positively correlated with BCC risk, while CTSS showed a negative correlation. Additionally, carfilzomib and L-glutamine were identified as existing compounds with potential therapeutic agents.
Conclusions: The strength of this study lies in its integrative approach, which not only enhances the reliability of the findings but also provides new possibilities for targeted drug development. Phe-MR analysis ensured the safety of the candidate genes and provided guidance for future targeted drug development. The results highlight the importance of further exploring these druggable genes and underscore the value of MR analysis in drug discovery, offering new therapeutic strategies for BCC and directions for future research.

Key words: basal cell carcinoma, pharmacogenomics, Mendelian randomization, eQTL, pQTL, phenome-wide MR analysis.

Introduction

Basal cell carcinoma (BCC) is one of the most common malignant skin tumors worldwide, with an incidence rate that has been increasing

annually, particularly among the elderly [1, 2]. It is estimated that more than 4 million new cases of BCC are diagnosed globally each year. With the intensification of population aging, the incidence of BCC in the elderly population is projected to increase by 48% by 2050 [3, 4]. Meanwhile, the cost of BCC treatment remains high. In the United States alone, annual expenditures for BCC treatment have exceeded 4.5 billion US dollars, and the treatment costs for recurrent or advanced cases are 6.4 times higher than those for early-stage cases [5–7].

Traditional BCC treatment methods mainly include surgical resection, radiotherapy, and photodynamic therapy [8–11]. Although these methods have shown some clinical efficacy, they also have many limitations [12, 13]. Surgical resection may lead to severe tissue trauma, radiotherapy may cause complications such as skin fibrosis, and the efficacy of photodynamic therapy is significantly limited by tumor depth and location. Given the limitations of these traditional treatment methods, the development of new therapeutic approaches is particularly urgent.

The pathogenesis of BCC is complex and diverse, mainly involving gene mutations and sun damage. Among them, the abnormal activation of the Hedgehog (HH) signaling pathway is one of the key driving factors for the occurrence of BCC. The abnormal activation of the HH pathway is usually manifested as inactivating mutations in PTCH1 (a tumor suppressor gene) (approximately 85–90% of sporadic BCCs have such mutations) or activating mutations in SMO (an oncogene) (approximately 10–20% of sporadic BCCs have such mutations), which in turn leads to the abnormal activation of the GLI (transcription factor) family, thereby promoting the development of BCC [14]. In addition, the HH pathway can also regulate the activity of GLI through non-canonical pathways (such as the EGFR, PI3K/AKT, and NF-κB signaling networks), bypassing the canonical HH-PTCH1-SMO activation pathway. Other gene mutations (such as inactivating mutations in LATS1/2 and PTPN14 in the Hippo-YAP pathway) and the activation of the WNT signaling pathway are also closely related to the occurrence of BCC.

With the in-depth understanding of the pathogenesis of BCC, targeted therapy has gradually attracted widespread attention as an emerging therapeutic strategy. Currently, inhibitors targeting the Hedgehog (Hh) signaling pathway (such as sonidegib and vismodegib) are applied in clinical practice. However, although these drugs have certain effects in the treatment of advanced BCC, the recurrence rate is high, especially in cases related to SMO mutations. In addition, adverse reactions are relatively common, with approximately 30% of patients discontinuing treatment due to toxic side effects, and the problem of drug resistance is also becoming increasingly prominent, with cross-resistance being relatively common. Therefore, identifying new drug targets and developing more effective drugs are of great significance for the treatment of BCC [15–17].

Against this background, the present study aimed to systematically identify potential druggable genes of BCC by integrating multi-omics data, including pharmacogenomics, transcriptomics, proteomics, and summary data from genome-wide association studies (GWAS). Based on these druggable genes, we further explored potential drug targets and available drugs, providing a solid theoretical basis for future drug development. Through this interdisciplinary research approach, we hope to provide new ideas and strategies for the precision treatment of BCC, thereby significantly improving patient prognosis.

Material and methods

Ethical approval

The current study strictly adhered to the steps outlined in the predetermined flowchart (Figure 1). In this study, the dataset we utilized is publicly accessible. The data had obtained the necessary informed consent from participants and had been approved by the appropriate ethical review in the original research. This study complied with the requirements of the Ethics Committee of Shandong Provincial Hospital, Shandong First Medical University, China (SWYX: No. 2019-115).

Related data sources

Drug genome

In this study, the sources of pharmacogenomic data were primarily twofold (Table I): First, we utilized the Drug-Gene Interaction Database (DGIdb v5.0.7, https:// www.dgidb.org/downloads) (Supplementary Tables SI) [18], a comprehensive online resource that consolidates drug-gene interaction information from various publications, databases, and other online resources. Second, we referred to the research by Finan *et al.* (Supplementary Table SII) [19]. which links the loci associated with complex diseases identified through GWAS to pharmacogenomics, providing significant scientific support for the identification and validation of druggable genes.

eQTL and pQTL datasets

Considering that cis-regulatory elements typically have more direct and specific effects on gene expression [20, 21], we prioritized the use of cis-expression quantitative trait loci (eQTL) and

Table I. Data sources

Type of dataset	Data subtype	Source	Sample size	Population	Download site
Druggable genome	DGIdb 4.0	Freshour SL, *et al.* 2020			https://www.dgidb.org/downloads.
	Prior druggable gene	Finan C, *et al.* 2017			Finan C, *et al.* PMID: 28356508.
QTL datasets	Blood cis-eQTL	eQTLGen Consortium	31684	European	https://eqtlgen.org/
	Skin cis-eQTL	eQTLGen Consortium	1980	European	https://yanglab.westlake.edu.cn/software/smr/
	Blood cis-pQTL	deCODE	35559	European	https://www.decode.com/summarydata/
GWAS summary	Basal cell carcinoma	GWAS Catalog	20506case : 314193con	European	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_C3_BASAL_b-CELL_CARCINOMA_EXALLC.gz
	1373Phenotypes	UK Biobank	408961	European	https://www.leelabsg.org/resources

DGIdb – drug-gene interaction database; eQTL – expression quantitative trait loci; eQTLGen Consortium – expression quantitative trait loci generation consortium; GTEx – genotype-tissue expression; GWAS – genome-wide association study; pQTL – protein quantitative trait loci.

cis-protein quantity trait loci (pQTL) data derived from human blood samples, which encompass genetic variations within a 1 Mb range flanking the druggable genomic coding sequences. Furthermore, to investigate the mechanisms of gene expression regulation in skin tissue, we also included cis-eQTL data for this tissue type (Table I).

The blood cis-eQTL data encompass transcriptome information for 16,989 genes from 31,684 individuals, sourced from the eQTLGen Consortium [22]. The blood cis-pQTL data, reported by Ferkingstad *et al*., include information on 4,907 proteins from 35,559 individuals. Additionally, we obtained cis-eQTL data for skin tissue from the Genotype-Tissue Expression (GTEx) Consortium (GTEx, V8), which include transcriptome information for genes across 517 samples [23].

GWAS dataset of BCC

In this study, we specifically focused on the genome-wide association study (GWAS) datasets related to BCC, sourced from the FinnGen project (https://r11.finngen.fi/pheno/C3_BASAL_CELL_CARCINOMA_EXALLC). We amassed GWAS summary data from 26,953 individuals.

Instrument choice

For the Mendelian randomization (MR) methodology, we meticulously selected single nucleotide polymorphisms (SNPs) that are strongly correlated with specific exposure factors as instrumental variables (IVs). To ensure the rigor and accuracy of MR analysis, the selected IVs had to strictly meet the following three key assumptions:

1. Relevance: The IV must have a significant correlation with the exposure of interest.
2. Independence: Once genetic variation is accounted for, the IV should be independent of potential confounders.
3. Exclusion restriction: The IV should not directly affect the outcome variable, except through the exposure factor [24].

Only when all three key assumptions are met can Mendelian randomization (MR) effectively serve as a tool for causal inference, providing us with compelling evidence regarding the causal relationship between exposure factors and outcomes.

We analyzed 6,889 potential pharmacogenomic loci, intersecting them with blood eQTL/pQTL data and skin tissue eQTL data to identify genetic variations closely associated with drug-gene expression (Figure 1). Subsequently, we focused on cis-variants located within a 1 Mb range of the drug-gene coding region to evaluate their direct impact on drug-gene expression.

To mitigate the potential interference of pleiotropy on our study outcomes and to ensure adherence to the assumptions of MR analysis, we established stringent selection criteria. We utilized a human blood eQTL genome-wide significance threshold ($p < 5 \times 10^{-8}$) and an *F*-statistic ≥ 10, while for human blood pQTL and skin tissue eQTL, we applied a genome-wide significance threshold ($p < 5 \times 10^{-5}$) [25, 26] and an *F*-statistic ≥ 10. Furthermore, we set the linkage disequilibrium (LD) coefficient r^2 to 0.001, the LD window width to 10 Mb, and employed the clumping function of the Two-Sample MR package to select appropriate IVs [27].

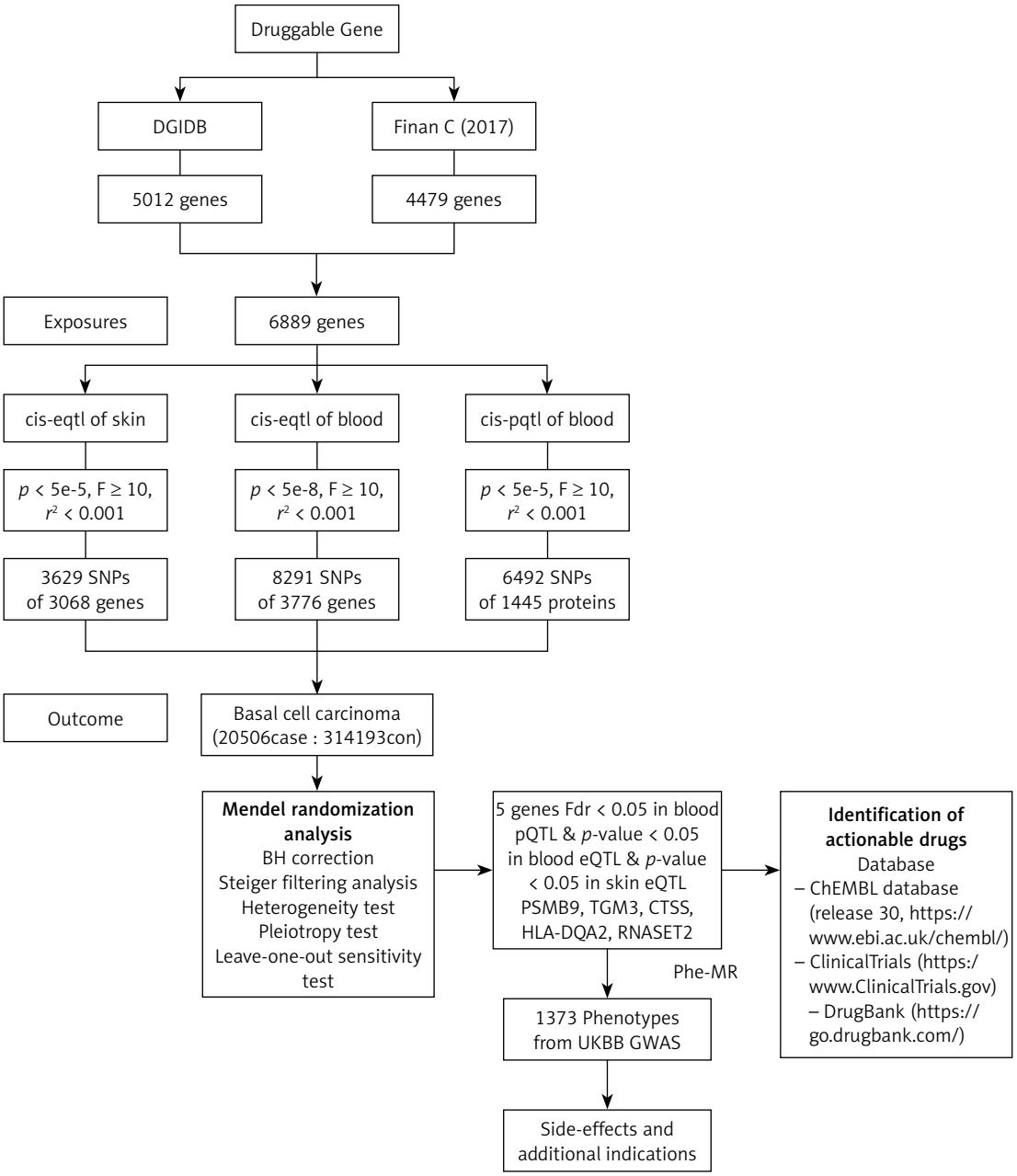


Figure 1. Research flowchart. Initially, we obtained 6,889 known druggable genes from the DGIdb database and the study by Finan *et al.* Subsequently, utilizing eQTL/pQTL data from human blood and skin tissues, we developed a tool targeting druggable genes to screen for independent genetic variants significantly associated with the expression of these genes (as instrumental variables, IV), primarily located within 1 Mb upstream and downstream of the coding region (cis). In the MR analysis, we preliminarily identified potential pathogenic genetic variants for basal cell carcinoma. Ultimately, we employed the Phe-MR method to assess the druggability of these 5 druggable genes and explored their potential for clinical development.

eQTL – expression quantitative trait loci, pQTL – protein quantitative trait loci, Phe-MR – phenome-wide Mendelian randomization analysis.

Mendelian randomization and Steiger filtering analysis

We employed the Wald ratio or inverse variance weighting (IVW) method to estimate the association between exposure and outcome within the framework of a random-effects model (REM) [28]. Furthermore, to control the false positive rate associated with multiple comparisons, we adjusted the *p*-values of the drug genes using the Benjamini-Hochberg procedure (BH correction), with a threshold set at a significance level of eQTL/pQTL Fdr < 0.05 [29].

In the process of conducting sensitivity analyses, we employed the MR Egger regression model to assess potential bias. This approach enables us

to quantify the extent to which our study results may be subject to bias and adjust our conclusions accordingly [30]. Additionally, we used the weighted mode and weighted median methods, both of which allow us to account for heterogeneity between studies, thereby providing an additional check on the stability of our results. Through these comprehensive analytical approaches, we can more thoroughly evaluate the reliability of our findings and evaluate potential sources of bias.

To assess heterogeneity among studies, we employed the IVW (inverse variance weighted) Q statistic. Furthermore, the intercept from the MR-Egger regression allowed us to evaluate potential pleiotropy issues. In the context of a GWAS, we applied the MR-PRESSO method to detect outliers [31, 32]. Any SNP (single nucleotide polymorphism) identified as a significant outlier during the analysis was removed. In the heterogeneity and pleiotropy analyses, $p < 0.05$ was considered statistically significant. Finally, by employing the Steiger filtering method through the TwoSampleMR R package, we could more accurately determine the direction of causality and reduce biases arising from reverse causation [21, 24, 33].

Our research findings are presented in the form of categorical variables to more clearly elucidate the direction of causality. Specifically, if the direction of effect from exposure to outcome was confirmed and the *p*-value was less than 0.05, it was marked as "true". Conversely, if the direction of effect reversed under the condition of $p < 0.05$, it was marked as "false". If $p \geq 0.05$, the result was considered indeterminate. To ensure the precision and consistency of the analysis, we employed R software (version 4.1.2) along with a suite of R packages including TwoSampleMR, MR-PRESSO, and RMediation to perform all data analyses.

Bayesian colocalization

Bayesian colocalization analysis is an advanced statistical technique aimed at investigating whether specific genetic variants exert a common association signal on two distinct traits (1: potential pharmacogenomics, 2: basal cell carcinoma) [34, 35]. This conclusion is drawn by evaluating the posterior probabilities of five different hypotheses:

PPH0: Neither trait is associated with genetic variants.

PPH1: Only trait 1 is associated with genetic variants.

PPH2: Only trait 2 is associated with genetic variants.

PPH3: Both traits are associated with genetic variants, but caused by different genetic variants.

PPH4: Both traits are associated with genetic variants, and caused by the same genetic variants.

When the posterior probability of hypothesis H4 exceeds 80%, it can be concluded that the potential pharmacogenomics shares the same genetic variants with BCC. To conduct Bayesian colocalization analysis, we used the 'coloc' package in R (http://cran.r-project. org/web/packages/coloc).

Phe-MR analysis

This study employed the phenome-wide Mendelian randomization (Phe-MR analysis) approach to explore the potential causal chains between identified pharmacogenomics and various disease traits. Through this analysis, we were able to assess the potential side effects of these genomes and investigate their possible applications in other medical conditions. Zhou *et al.* employed the SAIGE method – a highly efficient and accurate implementation of a generalized linear mixed model – to conduct an in-depth analysis of more than 1400 binary phenotype samples from 408,961 UK Biobank participants of European ancestry. Through SAIGE GWAS analysis (https:// www.leelabsg.org/ resource), we identified 1373 non-basal cell carcinoma diseases or traits (Table I and Supplementary Table SXII).

Actionable drugs

To identify potential candidate drugs targeting the selected pharmacogenomics, we conducted an exhaustive database search, including DrugBank (version 5.1.10, https:// go.drugbank.com), ChEMBL (version 33, https:// www.ebi.ac.uk/chembl), and ClinicalTrials.gov (https://www. clinicaltrials.gov). This process involved collecting detailed information about the drug molecules, the specific drug targets they act upon, and the current development status of these drugs in clinical trials.

Results

Druggable genome

To ensure that the pharmacogenomics we selected are not only reliable in data but also have the potential to become effective druggable genes, we followed these steps: First, we retrieved 5012 potential druggable genes from the DGIdb database (Supplementary Table SI) [18] version 5.0.7, a widely recognized resource that includes a vast array of gene information related to drug responses. Next, we referred to the study by Finan *et al.* (Supplementary Table SII) [19], from which we extracted 4479 pharmacogenomic data. To broaden our scope, we merged these two datasets, resulting in 6889 unique pharmacogenomics. To further enhance the accuracy and reliability of the data, we analyzed these genomes further, retaining those officially named by the Human

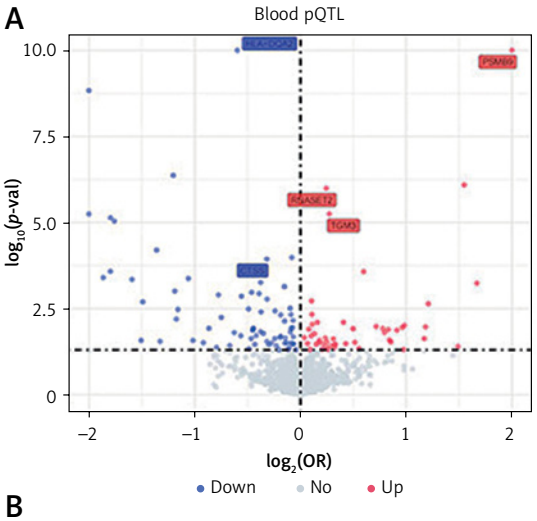
Genome Organisation's Gene Nomenclature Committee (HGNC). Through this series of selection and validation steps, we aimed to ensure the data quality of the selected pharmacogenomics and their potential as druggable genes (Supplementary Table SIII).

Candidate druggable genes

To identify genetic variations associated with a drug response, we undertook the following steps: First, we compared 6889 potential pharmacogenomics with human blood eQTL/pQTL and skin tissue eQTL datasets to identify overlapping genes. Subsequently, we extracted genetic variations from within 1 Mb regions upstream and downstream of the coding sequences of these overlapping druggable genes. After selecting and quality controlling the genetic variations, we screened 3629 SNPs from human skin tissue cis-eQTL data, which are associated with 3068 druggable genes (Supplementary Table SV). Similarly, we screened 8291 SNPs from human blood cis-eQTL data, which are associated with 3776 druggable genes (Supplementary Table SIV). Furthermore, we screened 6492 SNPs from human blood cis-pQTL data, which are associated with 1445 drug-expressing genes (Supplementary Table SVI). These selected SNPs will serve as instrumental variables (IVs), representing the exposure in MR analysis to assess the causal relationship between genetic variations and drug response (Figure 1).

Next, we conducted an MR analysis on the GWAS summary data for basal cell carcinoma. The analysis revealed potential causal associations between basal cell carcinoma and 366 druggable genes in skin tissue eQTL (Supplementary Table SVIII), 401 druggable genes in human blood eQTL (Supplementary Table SVII), and 121 druggable genes in human blood pQTL ($p < 0.05$) (Supplementary Table SIX). After adjusting for multiple testing, we identified 20 potential pharmacogenomic loci in human blood pQTL (BH correction Fdr < 0.05), 18 potential pharmacogenomic loci in human blood eQTL (BH correction Fdr < 0.05), and 57 potential pharmacogenomic loci in human skin eQTL (BH correction Fdr < 0.05) that showed a significant causal relationship with BCC (Supplementary Tables SVII–SIX).

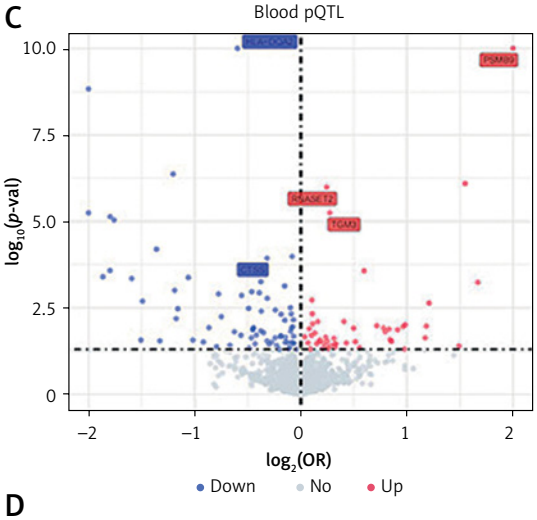
To enhance the precision and persuasiveness of our findings, we selected pharmacogenomics that exhibit significant causal relationships across three datasets as potential druggable genes for BCC of the skin. The specific criteria were: Fdr < 0.05 in blood pQTL, *p*-value < 0.05 in blood eQTL,



B

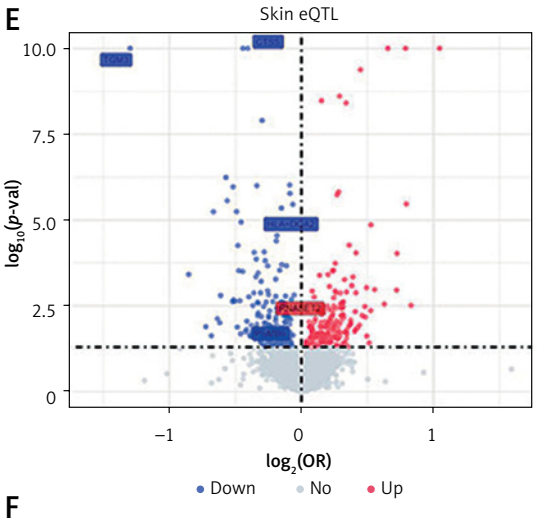
Type	Exposure	Method	nsnp	HR (95% CI)	*P*-value
RNASET2_blood_eqtl	ENSG00000026297	Inverse variance weighted	5	1.086 (1.045 to 1.129)	2.763×10^{-5}
HLA-DQA2_blood_eqtl	ENSG00000237541	Wald ratio	1	0.860 (0.802 to 0.923)	2.824×10^{-5}
PSMB9_blood_eqtl	ENSG00000240065	Inverse variance weighted	2	0.941 (0.899 to 0.985)	8.481×10^{-3}
CTSS_blood_eqtl	ENSG00000163131	Inverse variance weighted	2	0.792 (0.747 to 0.839)	3.697×10^{-15}
TGM3_blood_eqtl	ENSG00000125780	Inverse variance weighted	2	0.602 (0.541 to 0.670)	8.688×10^{-21}

Figure 2. Druggable genes associated with basal cell carcinoma etiology identified through MR and Bayesian colocalization analysis. **A** – Relationship between five druggable genes in blood pQTL and basal cell carcinoma. **B** illustrate the gene identifiers, research methods, number of SNPs, forest plots, confidence intervals of the OR values, and *p*-values for druggable genes in blood eQTL, blood pQTL, and skin eQTL, respectively. In all three datasets, the five druggable genes have passed Mendelian randomization and Bayesian colocalization analysis. Definition of OR value: If OR > 1, the exposure may promote the outcome; if OR < 1, the exposure may inhibit the outcome.



D

Type	Exposure	Method	nsnp	HR (95% CI)	*P*-value
CTSS_blood_pqtl	CTSS	Inverse variance weighted	5	0.801 (0.716 to 0.897)	1.155×10^{-4}
HLA-DQA2_blood_pqtl	HLA-DQA2	Inverse variance weighted	4	0.662 (0.585 to 0.749)	6.318×10^{-11}
PSMB9_blood_pqtl	PSMB9	Wald ratio	1	6.862 (4.098 to 11.492)	2.435×10^{-13}
RNASET2_blood_pqtl	RNASET2	Inverse variance weighted	6	1.183 (1.106 to 1.266)	1.022×10^{-6}
TGM3_blood_pqtl	TGM3	Inverse variance weighted	6	1.208 (1.113 to 1.311)	5.690×10^{-6}



F

Type	Exposure	Method	nsnp	HR (95% CI)	*P*-value
CTSS_skin_eqtl	ENSG00000163131	Inverse variance weighted	2	0.755 (0.704 to 0.809)	2.406×10^{-15}
HLA-DQA2_skin_eqtl	ENSG00000237541	Wald ratio	1	0.880 (0.829 to 0.934)	2.824×10^{-5}
PSMB9_skin_eqtl	ENSG00000240065	Wald ratio	1	0.916 (0.857 to 0.979)	9.460×10^{-3}
RNASET2_skin_eqtl	ENSG00000026297	Inverse variance weighted	3	1.070 (1.026 to 1.116)	1.746×10^{-3}
TGM3_skin_eqtl	ENSG00000125780	Wald ratio	1	0.407 (0.333 to 0.498)	2.565×10^{-18}

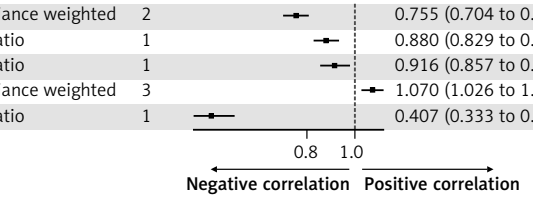


Figure 2. Cont. **C** – Relationship between five druggable genes in blood pQTL and basal cell carcinoma. **E** – Relationship between five druggable genes in skin eQTL and basal cell carcinoma. **D**, **F** illustrate the gene identifiers, research methods, number of SNPs, forest plots, confidence intervals of the OR values, and *p*-values for druggable genes in blood eQTL, blood pQTL, and skin eQTL, respectively. In all three datasets, the five druggable genes have passed Mendelian randomization and Bayesian colocalization analysis. Definition of OR value: If OR > 1, the exposure may promote the outcome; if OR < 1, the exposure may inhibit the outcome.

and p-value < 0.05 in skin eQTL. Given the close relationship between proteins and the physiological processes of diseases, to enhance the precision of our research findings, this study employed the Fdr as the statistical method of description. Ultimately, we identified five promising pharmacogenomics: PSMB9, TGM3, CTSS, HLA-DQA2, and RNASET2 (Supplementary Table SX and Figure 2).

Firstly, we observed that the transcriptional level of the RNASET2 gene is positively correlated with the risk of BCC in blood eQTL analysis (odds ratio (OR) = 1.183, 95% confidence interval CI: 1.106–1.266, $p = 1.02 \times 10^{-6}$), as well as in skin tissue (per 1 SD increase) (OR = 1.070, 95% CI: 1.026–1.116, $p = 1.75 \times 10^{-3}$). Additionally, in blood, the protein abundance of the RNASET2 gene correspondingly elevates the risk of BCC. As the expression level of the RNASET2 gene rises (per 1 SD increase), the risk of BCC increases accordingly.

Secondly, we found that the protein abundance of PSMB9 and TGM3 (per 1 SD increase) encoded by the corresponding genes is significantly positively correlated with the risk of BCC, with an increase in BCC risk. Specifically, the PSMB9 gene (OR = 6.862, 95% confidence interval CI: 4.098–11.492, $p = 2.43 \times 10^{-13}$) and TGM3 gene (OR = 1.208, 95% CI: 1.113–1.311, $p = 5.69 \times 10^{-6}$) both conform to this pattern. However, upon further analysis of the transcriptional levels of these two genes in the blood, the results showed that the transcriptional levels of PSMB9 (OR = 0.941, 95% CI: 0.899–0.985, $p = 8.48 \times 10^{-3}$) and TGM3 (OR = 0.602, 95% CI: 0.541–0.670, $p = 8.69 \times 10^{-21}$) are negatively correlated with BCC risk, meaning that as the transcriptional levels of these two genes increase (per 1 SD increase), the risk of BCC decreases. Additionally, an increase in the transcriptional level of PSMB9 (per 1 SD increase) in skin tissue (OR = 1.043, 95% CI: 1.010–1.076, $p = 9.46 \times 10^{-3}$) is associated with an increased risk of BCC; conversely, an increase in the transcriptional level of TGM3 (per 1 SD increase) in skin tissue (OR = 0.407, 95% CI: 0.333–0.498, $p = 2.56 \times 10^{-18}$) is associated with a decreased risk of BCC.

Lastly, we confirmed the association of CTSS and HLA-DQA2 genes (per 1 SD increase) with an increased risk of BCC across multiple distinct QTL datasets. Specifically, this includes the eQTL analysis in blood (CTSS: OR = 0.792, 95% confidence interval CI: 0.747–0.839, $p = 3.70 \times 10^{-15}$; HLA-DQA2: OR = 0.860, 95% CI: 0.802–0.923, $p = 2.76 \times 10^{-5}$), the pQTL analysis in blood (CTSS: OR = 0.801, 95% CI: 0.716–0.897, $p = 1.15 \times 10^{-4}$; HLA-DQA2: OR = 0.662, 95% CI: 0.585–0.749, $p = 6.32 \times 10^{-11}$), and the eQTL analysis in skin tissue (CTSS: OR = 0.755, 95% CI: 0.704–0.809, $p = 2.41 \times 10^{-15}$; HLA-DQA2: OR = 0.880, 95% CI: 0.829–0.934, $p = 2.82 \times 10^{-5}$) (Figure 2 and Supplementary Tables SVII–SIX).

Phe-MR analysis of BCC candidate druggable genes

We conducted a Phe-MR analysis on 1373 diseases and traits from the UK Biobank (Supplementary Table SXII). In this analysis, the IVs we used were consistent with those previously identified to be associated with traits related to BCC of the skin, involving 15 SNPs across 5 pharmacogenes (for details, see Supplementary Table SXI). In the Phe-MR analysis, statistical significance was considered if the adjusted Fdr < 0.05 (BH-adjusted). Our study found that upregulation of the RNASET2 gene may reduce the risk of certain diseases. Specifically, upregulation of the RNASET2 gene in blood and skin was associated with lower risk of hypothyroidism (OR = 0.83, 0.85, respectively) and hypothyroidism NOS (OR = 0.82, 0.84, respectively), and upregulation of the RNASET2 gene in skin (OR = 0.78) was associated with lower risk of thyrotoxicosis with or without goiter. Similarly, upregulation of RNASET2 in the skin (OR = 0.78) was associated with lower risk of thyrotoxicosis with or without goiter. Furthermore, we found that increased expression of the PSMB9 gene in the blood (OR = 0.59) and skin (OR = 0.47) may be associated with reduced risk of iron metabolism disorders. It is also noteworthy that increased expression of the PSMB9 gene in the blood (OR = 0.73) and skin (OR = 0.63) was associated with a reduced risk of multiple sclerosis.

The results of the Phe-MR analysis further indicate that a decrease in the expression level of the PSMB9 gene may be associated with reduced risk of other diseases such as asthma (blood OR = 1.09, skin OR = 1.13), chronic hepatitis (blood OR = 1.87), hypothyroidism (blood OR = 1.59, skin OR = 1.23), type 1 diabetes (blood OR = 1.48, skin OR = 1.77), and celiac disease (blood OR = 3.27, skin OR = 5.75). Notably, downregulation of RNASET2 and PSMB9 genes is associated with a reduced risk of BCC. This implies that drug targeting of RNASET2 and PSMB9 may not only be beneficial for BCC but could also have a positive impact on certain diseases. However, the other three genes (TGM3, CTSS, HLA-DQA2) are not related to 1373 diseases and traits (Supplementary Table SXIII), indicating that drugs targeting these genes may not have potential side effects (Supplementary Table SXIII).

Actionable drugs

In our study, the preclinical or clinical development activities of five potential pharmacological targets for BCC were assessed (Table II). Although formulations related to the PSMB9, TGM3, and CTSS genes have been evaluated in clinical trials for other diseases, they have not yet been used

for the treatment of BCC. To date, we have not found any drugs related to the HLA-DQA2 gene. Formulations related to the RNASET2 gene are currently in the experimental stage. Carfilzomib, which inhibits expression of the PSMB9 gene, has shown potential in the treatment of BCC. On the other hand, L-glutamine, as a substrate of TGM3, may significantly affect the tumor immune microenvironment and the effectiveness of immunotherapy by regulating the activity of TGM3 in the tumor microenvironment. However, fostamatinib and petesicatib, which are inhibitors and antagonists of CTSS, respectively, may not be ideal drug choices, as their mechanisms of

Table II. Actionable drugs. Information on operable drugs involving four druggable genes, along with the molecular functions of these genes

Druggable gene	Molecule type	Compounds	Action type	Clinical development activities	Druggable gene molecular function
RNASET2	Small molecule	Adenosine 3',5'-diphosphate	*	Experimental	This ribonuclease gene is a novel member of the Rh/T2/S-glycoprotein class of extracellular ribonucleases. It is a single copy gene that maps to 6q27, a region associated with human malignancies and chromosomal rearrangement.
	Small molecule	Adenosine-2'-5'-diphosphate	*	Experimental	
PSMB9	Small molecule	Carfilzomib	Inhibitor	Carfilzomib-approved, investigational • For the treatment of adults with relapsed or refractory multiple myeloma	The proteasome is a multicatalytic proteinase complex with a highly ordered ring-shaped 20S core structure. This gene is located in the class II region of the MHC (major histocompatibility complex).
CTSS	Small molecule	Ethanol	Inhibitor	Ethanol: approved • Topical disinfectant • Pharmaceutical solvent/ preservative/alcoholic beverage iongredient	The preproprotein encoded by this gene, a member of the peptidase C1 family, is a lysosomal cysteine proteinase that participates in the degradation of antigenic proteins to peptides for presentation on MHC class II molecules.
	Small molecule	Fostamatinib	Inhibitor	Fostamatinib-approved, investigational • Used for the treatment of rheumatoid arthritis and ITP. • Potential treatment for controlling ARDS in severe COVID-19 patients.	
TGM3	Small molecule	5'-guanosine-diphosphate-monothiophosphate	*	Experimental	Transglutaminases are enzymes that catalyze the crosslinking of proteins by epsilon-gamma glutamyl lysine isopeptide bonds.
	Small molecule	Guanosine-5'-monophosphate	*	Experimental	
	Small molecule	B-2-octylglucoside	*	Experimental	
	Small molecule	Guanosine-5'-diphosphate	*	Experimental	
	Small molecule	L-glutamine	Substrate	L-glutamine: approved, investigational, nutraceutical • It is a non-essential amino acid. • Used for the treatment of sickle cell disease.	

action may be contrary to the desired effects for the treatment of BCC.

Discussion

In our study, by integrating and analyzing the data, we have obtained preliminary evidence for the genetic association between five druggable genes – PSMB9, TGM3, CTSS, HLA-DQA2, RNASET2 – and BCC. Pharmacogenetic analysis indicates that PSMB9 and RNASET2 may be associated with adverse effects during treatment. In assessing the therapeutic potential of drugs targeting these genes, we found that carfilzomib may treat BCC by inhibiting PSMB9. Furthermore, L-glutamine, as a substrate of TGM3, may influence the progression of the disease by modulating its activity.

The PSMB9 proteasome, a multicatalytic proteinase complex located in the MHC class II region, plays a crucial role in the immune response [36]. It degrades aberrant proteins and generates antigenic peptides, promoting antigen presentation by MHC class I molecules and activating T-cell responses. Furthermore, increased expression of PSMB9 is associated with better prognosis in cancer patients, helping to enhance the presentation of tumor antigens and improving the immune system's ability to recognize and eliminate cancer cells [37]. Although the relationship between PSMB9 and BCC is not yet fully understood, PSMB9 may play a role in BCC through similar mechanisms, and further research is needed to establish a direct link between the two. It is important to note that our Phe-MR analysis did not show significant adverse reactions associated with PSMB9. On the contrary, we found that increased expression of PSMB9 may reduce the risk of iron metabolism disorders and multiple sclerosis. Carfilzomib, an inhibitor of the PSMB9 gene, is currently used in clinical settings to treat patients with relapsed or refractory multiple myeloma [38].

TGM3 (transglutaminase 3) is a calcium-dependent enzyme that plays a crucial role in the physiological processes of the skin and hair follicles, particularly in cell differentiation, proliferation, and apoptosis [39]. Studies have shown that TGM3 is involved in the regulation of cell proliferation, migration, and invasion, and may promote epithelial-mesenchymal transition (EMT) by activating signaling pathways such as PI3K/AKT, MAPK/ERK, and NF-κB, thereby facilitating tumor development [40, 41]. Our research indicates that an increase in TGM3 protein abundance may be associated with an increased risk of BCC. Although the potential mechanism of TGM3 in BCC is not fully elucidated, some studies provide possible clues. In BCC, the expression pattern of TGM3 is different from that in normal skin, showing strong staining in the cytoplasm and nucleus, and its expression level is significantly upregulated in BCC, but downregulated in other types of skin cancer [42]. This suggests that the expression pattern of TGM3 may make it a potential specific marker for BCC diagnosis, and TGM3 may play a role in the development of BCC by affecting cell proliferation, differentiation, and migration processes [43]. Over 90% of BCCs exhibit genetic activation of the Hedgehog (HH) signaling pathway [44]. However, studies have shown that TGM3 may be regulated by the HH signaling pathway through the GLI2 transcription factor [42]. In addition, L-glutamine is a common amino acid in total parenteral nutrition, which is very important for various physiological processes such as intestinal health, immune system function, and cell repair [45].

The CTSS gene encodes cathepsin S, a protein that plays a crucial role in a variety of physiological and pathological processes. Although the relationship between CTSS and BCC is not yet fully understood, studies have indicated that the expression of CTSS in BCC is closely associated with the tumor's invasiveness and metastatic potential. CTSS facilitates the spread of tumor cells by promoting angiogenesis and degrading the extracellular matrix surrounding the tumor, thus potentially playing a role in the invasive process of tumor cells [46]. Furthermore, the activity of CTSS varies among different subtypes of BCC, suggesting that it may play a key role in the process of tumor invasion. Therefore, the expression level of CTSS could serve as a prognostic marker for BCC, aiding in timely recognition, treatment, and prevention [47]. Currently, research on CTSS inhibitors is underway, which may offer new strategies for the treatment of BCC.

The HLA-DQA2 gene, a key component of the major histocompatibility complex (MHC) class II molecules, plays an essential role in immune responses [48]. Studies have indicated that HLA-DQA2 is crucial for immune surveillance and is associated with susceptibility to basal cell carcinoma (BCC) [49]. Tumor cells may evade immune surveillance by downregulating the expression levels of HLA-DQA2 and other MHC molecules, reducing the presentation of tumor-specific antigens, and thus decreasing the recognition and attack of tumor cells by T cells. Furthermore, the expression level of HLA-DQA2 may also regulate the infiltration and function of immune cells in the tumor microenvironment, thereby affecting the growth and metastatic potential of tumors [50]. Our study found a negative correlation between the HLA-DQA2 gene and basal cell carcinoma. This finding suggests that finely tuning the activity or expression of HLA-DQA2 may help inhibit the growth and spread of tumor cells, thereby improving therapeutic outcomes.

The RNASET2 gene belongs to the Rh/T2/S-glycoprotein family, encoding an enzyme with ribonuclease activity, and is located in the 6q27 chromosomal region, which is associated with human malignant tumors and chromosomal rearrangements [51]. RNASET2 plays a role in anti-angiogenesis and immune regulation in tumor development, potentially limiting tumor growth and metastasis by inhibiting angiogenesis [52]. Although a direct relationship between RNASET2 and basal cell carcinoma (BCC) has not been previously established, recent studies suggest that RNASET2 may promote the development of BCC by affecting the tumor microenvironment and cellular stress responses. In some studies, RNASET2 has been highlighted as an effective biomarker and therapeutic target for BCC across the full phenotypic spectrum of human diseases [53]. However, no drugs specifically targeting the RNASET2 gene have been developed to date. Given the key role of the RNASET2 gene in multiple physiological processes, the development of drugs targeting the RNASET2 gene may offer potential therapeutic advantages for the treatment of basal cell carcinoma.

The strengths of this study lie in its rigorous methodology and in-depth data analysis. Firstly, we utilized genetic variations as instrumental variables, effectively reducing the impact of confounding factors, and thereby providing more precise causal inferences. Secondly, this study not only combined genetic and protein expression analyses but also integrated data from GWAS of basal cell carcinoma, further enhancing the persuasiveness of the results. Crucially, we conducted meticulous multiple corrections on our results, employed Bayesian co-localization analysis, and performed cross-validation on multiple independent datasets. This not only enhanced the credibility of our conclusions but also ensured the robustness, accuracy, and universality of our findings. Lastly, through pharmacogenetic analysis (Phe-MR), we were able to predict adverse drug events, optimize drug usage, and protect patient health. This provides new perspectives and strategies for the prevention and treatment of basal cell carcinoma.

While this study shows significant potential in the field of pharmacogenomics, it also inevitably presents some challenges and limitations. Firstly, the accuracy of MR analysis depends on the appropriateness of the selected SNPs as instrumental variables, which need to meet specific assumptions. Secondly, the genetic heterogeneity across different ethnicities and populations may limit the universality of MR analysis, affecting the generalizability of the results, and caution should be exercised in their application. It is important to note that MR analysis is an innovative method for exploring the links between drugs and diseases, but it serves only as a supplementary tool and cannot replace the traditional drug development process. The safety, efficacy, and applicability of drugs need to be verified through rigorous clinical trials and evaluations. In future drug development, we look forward to MR analysis being combined with traditional methods to jointly promote drug repurposing and the discovery of new druggable genes. At the same time, we will continue to optimize and improve MR analysis methods to enhance their value and accuracy in drug development.

This study is based purely on data analysis, and the conclusions drawn will require subsequent experimental validation. Based on these conclusions, we can use cellular and animal models to evaluate the *in vivo* and *in vitro* efficacy and safety of the PSMB9 inhibitor carfilzomib and the TGM3 substrate L-glutamine. This can be further confirmed through prospective clinical trials to assess their clinical applicability. We have integrated data from 26,953 GWAS samples, eQTL/pQTL, and Phe-MR triple evidence, which significantly reduces the false-positive rate (FDR < 0.05). Compared with traditional high-throughput screening, this strategy is less costly and has a shorter duration, providing a rapid decision-making basis for pharmaceutical companies and clinical practice. If validated successfully, it can be directly advanced to the preclinical or repurposing stage, maximizing translational efficiency.

In conclusion, our study offers new perspectives for the future treatment of basal cell carcinoma, highlighting the importance of five identified druggable genes (PSMB9, TGM3, CTSS, HLA-DQA2, RNASET2) as potential therapeutic targets, and emphasizing the necessity for in-depth research on these druggable genes. Carfilzomib, which inhibits expression of the PSMB9 gene, shows significant potential in the treatment of basal cell carcinoma. L-glutamine may play a role in the tumor microenvironment by regulating the activity of TGM3. Through Phe-MR analysis, we revealed potential causal relationships between identified pharmacogenomics and a broad range of disease traits, which will help in predicting the side effects of druggable genes and exploring their potential applications in other medical conditions.

Funding

Shandong Provincial Natural Science Foundation (ZR2023MH088 and ZR2020MH219).

Ethical approval

This study complied with the requirements of the Ethics Committee of Shandong Provincial Hospital, Shandong First Medical University, China (SWYX: No. 2019-115).

Conflict of interest

The authors declare no conflict of interest.

References

1. Sethi A, Vogt M, Brocato J, Habeeb L, Squittieri N. Comment on "Basal cell carcinoma: Contemporary approaches to diagnosis, treatment, and prevention". J Am Acad Dermatol 2023; 88: e29-30.
2. Sobjanek M, Zabłotna M, Michajłowski I, Nedoszytko B, Lesiak A, Nowicki R. -308 G/A TNF-αgene polymorphism influences the course of basal cell carcinoma in a Polish population. Arch Med Sci 2015; 11: 599-604.
3. Untaaveesup S, Dendumrongsup W, Srichana P, et al. Clinical outcomes and adverse events of Hedgehog pathway inhibitors for advanced basal cell carcinoma patients: a systematic review and meta-analysis. Heliyon 2025; 11: e39476.
4. Wang R, Chen Y, Shao X, et al. Burden of skin cancer in older adults from 1990 to 2021 and modelled projection to 2050. JAMA Dermatol 2025; 161: 715-22.
5. Pan Y, Tang B, Guo Y, Cai Y, Li YY. Global burden of non-melanoma skin cancers among older adults: a comprehensive analysis using machine learning approaches. Sci Rep 2025; 15: 15266.
6. Zhou L, Zhong Y, Han L, Xie Y, Wan M. Global, regional, and national trends in the burden of melanoma and non-melanoma skin cancer: insights from the global burden of disease study 1990-2021. Sci Rep 2025; 15: 5996.
7. Si Z, Ying J, Zhou Y. A study on the global burden of non-melanoma skin cancer from 1990 to 2019. Arch Med Sci 2024; 20: 1902-8.
8. McDaniel B, Steele RB. StatPearls. editors. ed. Treasure Island (FL): 2025.
9. Kilgour JM, Jia JL, Sarin KY. Review of the molecular genetics of basal cell carcinoma; inherited susceptibility, somatic mutations, and targeted therapeutics. Cancers (Basel) 2021; 13: 3870.
10. Cameron MC, Lee E, Hibler BP, et al. Basal cell carcinoma: epidemiology; pathophysiology; clinical and histological subtypes; and disease associations. J Am Acad Dermatol 2019; 80: 303-17.
11. Lesiak A, Slowik-Rylska M, Rogowski-Tylman M, Sysa-Jedrzejowska A, Norval M, Narbutt J. Risk factors in Central Poland for the development of superficial and nodular basal cell carcinomas. Arch Med Sci 2010; 6: 270-5.
12. Miller SJ. Biology of basal cell carcinoma (Part I). J Am Acad Dermatol 1991; 24: 161-75.
13. Basset-Seguin N, Herms F. Update in the management of basal cell carcinoma. Acta Derm Venereol 2020; 100: adv00140.
14. Draper E, Li YY, Mahadevan NR, Laga AC, Hanna J, Russell-Goldman E. Clinicopathologic and molecular characterization of basal cell carcinoma arising at sun-protected sites. Am J Surg Pathol 2025; 49: 328-35.
15. Peris K, Fargnoli MC, Garbe C, et al. Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. Eur J Cancer 2019; 118: 10-34.
16. Schmults CD, Blitzblau R, Aasi SZ, et al. Basal Cell Skin Cancer, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2023; 21: 1181-203.
17. Danial C, Sarin KY, Oro AE, Chang AL. An investigator-initiated open-label trial of sonidegib in advanced basal cell carcinoma patients resistant to vismodegib. Clin Cancer Res 2016; 22: 1325-9.
18. Freshour SL, Kiwala S, Cotto KC, et al. Integration of the Drug-Gene Interaction Database (DGIdb 4.0) with open crowdsource efforts. Nucleic Acids Res 2021; 49: D1144-51.
19. Finan C, Gaulton A, Kruger FA, et al. The druggable genome and support for target identification and validation in drug development. Sci Transl Med 2017; 9: eaag1166.
20. Emilsson V, Ilkov M, Lamb JR, et al. Co-regulatory networks of human serum proteins link genetics to disease. Science 2018; 361: 769-73.
21. Yin KF, Chen T, Gu XJ, et al. Systematic druggable genome-wide Mendelian randomization identifies therapeutic targets for sarcopenia. J Cachexia Sarcopenia Muscle 2024; 15: 1324-34.
22. The GTEx Consortium atlas of genetic regulatory effects across human tissues. Science 2020; 369: 1318-30.
23. Ferkingstad E, Sulem P, Atlason BA, et al. Large-scale integration of the plasma proteome with genetics and disease. Nat Genet 2021; 53: 1712-21.
24. Relton CL, Davey Smith G. Two-step epigenetic Mendelian randomization: a strategy for establishing the causal role of epigenetic processes in pathways to disease. Int J Epidemiol 2012; 41: 161-76.
25. Shu M, Yates TB, John C, et al. Providing biological context for GWAS results using eQTL regulatory and co-expression networks in Populus. New Phytol 2024; 244: 603-17.
26. Sun X, Chen B, Qi Y, et al. Multi-omics Mendelian randomization integrating GWAS, eQTL and pQTL data revealed GSTM4 as a potential drug target for migraine. J Headache Pain 2024; 25: 117.
27. Carter AR, Gill D, Davies NM, et al. Understanding the consequences of education inequality on cardiovascular disease: mendelian randomisation study. BMJ 2019; 365: l1855.
28. Yao M, Mei F, Zou K, Li L, Sun X. A Bayesian bias-adjusted random-effects model for synthesizing evidence from randomized controlled trials and nonrandomized studies of interventions. J Evid Based Med 2024; 17: 550-8.
29. Liang YY, Zhou M, He Y, et al. Observational and genetic evidence disagree on the association between loneliness and risk of multiple diseases. Nat Hum Behav 2024; 8: 2209-21.
30. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 2015; 44: 512-25.
31. Andersen JV, Christensen SK, Aldana BI, Nissen JD, Tanila H, Waagepetersen HS. Alterations in cerebral cortical glucose and glutamine metabolism precedes amyloid plaques in the APPswe/PSEN1dE9 mouse model of Alzheimer's disease. Neurochem Res 2017; 42: 1589-98.
32. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet 2018; 50: 693-8.
33. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. PLoS Genet 2017; 13: e1007081.
34. Wu S, Meena D, Yarmolinsky J, et al. Mendelian randomization and bayesian colocalization analysis implicate glycoprotein VI as a potential drug target for cardioembolic stroke in South Asian populations. J Am Heart Assoc 2024; 13: e035008.

35. Giambartolomei C, Vukcevic D, Schadt EE, et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. PLoS Genet 2014; 10: e1004383.
36. Jhunjhunwala S, Hammer C, Delamarre L. Antigen presentation in cancer: insights into tumour immunogenicity and immune evasion. Nat Rev Cancer 2021; 21: 298-312.
37. Rouette A, Trofimov A, Haberl D, et al. Expression of immunoproteasome genes is regulated by cell-intrinsic and -extrinsic factors in human cancers. Sci Rep 2016; 6: 34019.
38. Georgoulis V, Haidich AB, Bougioukas KI, Hatzimichael E. Efficacy and safety of carfilzomib for the treatment of multiple myeloma: an overview of systematic reviews. Crit Rev Oncol Hematol 2022; 180: 103842.
39. Zhang W, Wu C, Zhou K, et al. Clinical and immunological characteristics of TGM3 in pan-cancer: a potential prognostic biomarker. Front Genet 2022; 13: 993438.
40. Feng Y, Ji D, Huang Y, et al. TGM3 functions as a tumor suppressor by repressing epithelial-to-mesenchymal transition and the PI3K/AKT signaling pathway in colorectal cancer. Oncol Rep 2020; 43: 864-76.
41. Hu JW, Yang ZF, Li J, et al. TGM3 promotes epithelial-mesenchymal transition and hepatocellular carcinogenesis and predicts poor prognosis for patients after curative resection. Dig Liver Dis 2020; 52: 668-76.
42. Smirnov A, Anemona L, Montanaro M, et al. Transglutaminase 3 is expressed in basal cell carcinoma of the skin. Eur J Dermatol 2019; 29: 477-83.
43. Chermnykh ES, Alpeeva EV, Vorotelyak EA. Transglutaminase 3: the involvement in epithelial differentiation and cancer. Cells 2020; 9: 1996.
44. Savoia P, Veronese F, Camillo L, Tarantino V, Cremona O, Zavattaro E. Multiple basal cell carcinomas in immunocompetent patients. Cancers (Basel) 2022; 14: 3211.
45. Cluntun AA, Lukey MJ, Cerione RA, Locasale JW. Glutamine metabolism in cancer: understanding the heterogeneity. Trends Cancer 2017; 3: 169-80.
46. Smyth P, Sasiwachirangkul J, Williams R, Scott CJ. Cathepsin S (CTSS) activity in health and disease - a treasure trove of untapped clinical potential. Mol Aspects Med 2022. 88: 101106.
47. Li Y, Li Q, Cao Z, Wu J. Multicenter proteome-wide Mendelian randomization study identifies causal plasma proteins in melanoma and non-melanoma skin cancers. Commun Biol 2024; 7: 857.
48. Schaafsma E, Fugle CM, Wang X, Cheng C. Pan-cancer association of HLA gene expression with cancer prognosis and immunotherapy efficacy. Br J Cancer 2021; 125: 422-32.
49. Aboulaghras S, Piancatelli D, Taghzouti K, et al. Meta-analysis and systematic review of HLA DQ2/DQ8 in adults with celiac disease. Int J Mol Sci 2023; 24: 1188.
50. Adolphe C, Xue A, Fard AT, Genovesi LA, Yang J, Wainwright BJ. Genetic and functional interaction network analysis reveals global enrichment of regulatory T cell genes influencing basal cell carcinoma susceptibility. Genome Med 2021; 13: 19.
51. Bruno A, Noonan DM, Valli R, et al. Human RNASET2: a highly pleiotropic and evolutionary conserved tumor suppressor gene involved in the control of ovarian cancer pathogenesis. Int J Mol Sci 2022; 23: 9074.
52. Liu Y, Zhang Z, Xi P, et al. Systematic analysis of RNASET2 gene as a potential prognostic and immunological biomarker in clear cell renal cell carcinoma. BMC Cancer 2023; 23: 837.
53. Han QJ, Zhu YP, Sun J, Ding XY, Wang X, Zhang QZ. PTGES2 and RNASET2 identified as novel potential biomarkers and therapeutic targets for basal cell carcinoma: insights from proteome-wide mendelian randomization, colocalization, and MR-PheWAS analyses. Front Pharmacol 2024; 15: 1418560.