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RESEARCH ARTICLE

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Mining database for the clinical significance and prognostic value of CBX family in skin cutaneous melanoma

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Abstract

Background: Skin cutaneous melanoma (SKCM) is one of the most aggressive malignancies with high invasiveness. Chromobox (CBX) family are involved in the regulation of the tumorigenesis, progression, invasion, and apoptosis of many malignancies.

Methods: The clinical significance and prognostic value of CBX family in SKCM were analyzed via a series of databases, including ONCOMINE, GEPIA, UALCAN, TIMER, GSCALite, DAVID 6.8, GeneMANIA, and LinkedOmics.

Results: We found that the level of CBX2, CBX3, CBX5, and CBX6 was upregulated while the level of CBX7 and CBX8 was downregulated in tumor tissues in SKCM. Moreover, the mRNA expression of CBX1 and CBX2 was significantly associated with the pathological stage in SKCM. Prognosis analysis revealed that SKCM patients with high CBX5 level and low CBX7 level had a poor prognosis. Immune infiltrations analysis revealed that the expression of CBX family was associated with the abundance of certain immune cells in SKCM. We also found that CBX family were associated with the activation of cell cycle pathway and DNA damage response, and the inhibition of apoptosis pathway. Moreover, enrichment analysis revealed that CBX family and correlated genes were enriched in chromatin modification, PcG protein complex, transcription coactivator activity, protein binding, and RNA splicing. Several Kinase targets (ATM, CDK1, and PLK1) and miRNA targets (MIR-331, MIR-296, and MIR-496) of CBX family were also identified.

Conclusion: Our study may uncover CBX family–associated molecular mechanisms involved in the tumorigenesis and progression of SKCM and provide additional choice for the prognosis and therapy biomarker for SKCM.

KEYWORDS

biomarker, CBX family, prognosis, SKCM

1 | INTRODUCTION

Skin cutaneous melanoma (SKCM) is one of the most aggressive malignancies originated from skin melanocytes.[1] About 200 000 cases are initially diagnosed with SKCM each year, accounting for over 90% of new skin cancers and causing about 3/4 of skin-related deaths.[2] Localized SKCM is managed and curative.[3] However, patients with localized SKCM trend to be with metastasis due to the

high invasiveness.[4] Once SKCM patients have metastasis or in the advance stages of the disease, the prognosis is poor.[5] Thus, these sobering data illustrate a critical need for novel biomarkers related to the prognosis and therapy of SKCM.

Increasing evidences revealed that aberration of epigenetic regulation was critical for the regulation of gene and noncoding RNA expression, thus affecting the pathogenesis and progression of cancers, including SKCM.[6-8] Polycomb group (PcG) complexes were epigenetic regulatory complexes, dysregulation of which has been associated with many cancer types.[9] Chromobox (CBX) family proteins were canonical components of PcG.[10] A total of eight members of CBX family (CBX1/2/3/4/5/6/7/8) had been identified in human genome.[11] By mediating the differentiation and self-renewal of tumor stem cells, CBX family were involved in the regulation of roles in tumorigenesis, progression, invasion, and apoptosis of malignancies.[11,12] Moreover, CBX family were suggested as prognostic biomarkers for certain types of cancers, including breast cancer and hepatocellular carcinoma.[10,11] However, the functions of CBX family were far from fully clarified.

Our study aimed to systematically explore the gene expression, prognostic value, immune correlations, and potential functions of CBX family in SKCM. Our study may uncover CBX family–associated molecular mechanisms in the tumorigenesis and progression of SKCM and provide additional choice for the prognosis and therapy biomarker for SKCM.

2 | MATERIALS AND METHODS

2.1 | Oncomine

Oncomine(www.oncomine.org), a comprehensive gene analysis tools, could be used to transcriptome data analysis based on 715 datasets and 86 733 samples.[13] In current study, the level of CBX family in melanoma was analyzed by the Oncomine, with a P-value of 0.05, a fold change (FC) of 1.5, and a gene rank of Top 10%.

2.2 | GEPIA

GEPIA (http://gepia.cancer-pku.cn) is a bioinformatics analysis tool, providing various analyses, such as gene expression analysis, prognostic analysis, and correlation analysis.[14] In GEPIA, we explored the expression of CBX family in tumor tissues and normal tissues, as well as in different pathological stage with TCGA_SKCM datasets. $P < .05$ indicates statistical significance.

2.3 | UALCAN

UALCAN (http://ualcan.path.uab.edu) is a bioinformatics analysis tool, providing various analyses, such as gene expression analysis, prognostic analysis, and correlation analysis.[15] The prognosis of CBX family in SKCM was explored with UALCAN using TCGA_SKCM datasets. $P < .05$ indicates statistical significance.

2.4 | GSCALite

GSCALite (http://bioinfo.life.hust.edu.cn/web/GSCALite/) is a web-based analysis platform for gene set cancer analysis, including mRNA, SNV, methylation, cancer pathway activity, and drug analysis.[16] The single nucleotide variation (SNV) summary and oncoplot waterfall plot were generated by maftools. The Spearman correlation was performed to explore the correlation between the expression of CBX family and 265 small molecules or drugs from Genomics of Drug Sensitivity in Cancer (GDSC). These analyses were performed using TCGA_SKCM datasets, and P-value $< .05$ was considered as significant.

2.5 | TIMER

TIMER (http://www.genemania.org) is an immune infiltrates analysis tool could provide various analyses with the dataset of 10 897 samples.[17] CBX family expression and its correlation with the abundance of immune cells and gene markers expression were evaluated using Spearman's correlation with TCGA_SKCM datasets. The infiltration level for each somatic copy number alterations (SCNA) category was compared with the normal using a two-sided Wilcoxon rank-sum test.

2.6 | DAVID 6.8

Enrichment analysis of CBX family, including GO and KEGG pathway, was performed using DAVID 6.8 (https://david.ncifcrf.gov/). We first extracted the top ten genes correlated with each member of CBX family in GEPIA. After, we submitted CBX family and correlated genes to DAVID 6.8. And the results were visualized with R project using a “ggplot2” package with a p-value of 0.05.

2.7 | GeneMANIA

GeneMANIA (http://www.genemania.org) is a flexible portal which could analyze the functions of gene lists and find neighboring genes associated with gene lists by constructing protein-protein interaction (PPI) network.[18]

2.8 | LinkedOmics

LinkedOmics (http://www.linkedomics.org) is a flexible portal which could perform a comprehensive and systematic analysis of cancer transcriptional data.[19] The Kinase target and miRNA target analyses of CBX family in SKCM were conducted with “Link-Interpreter

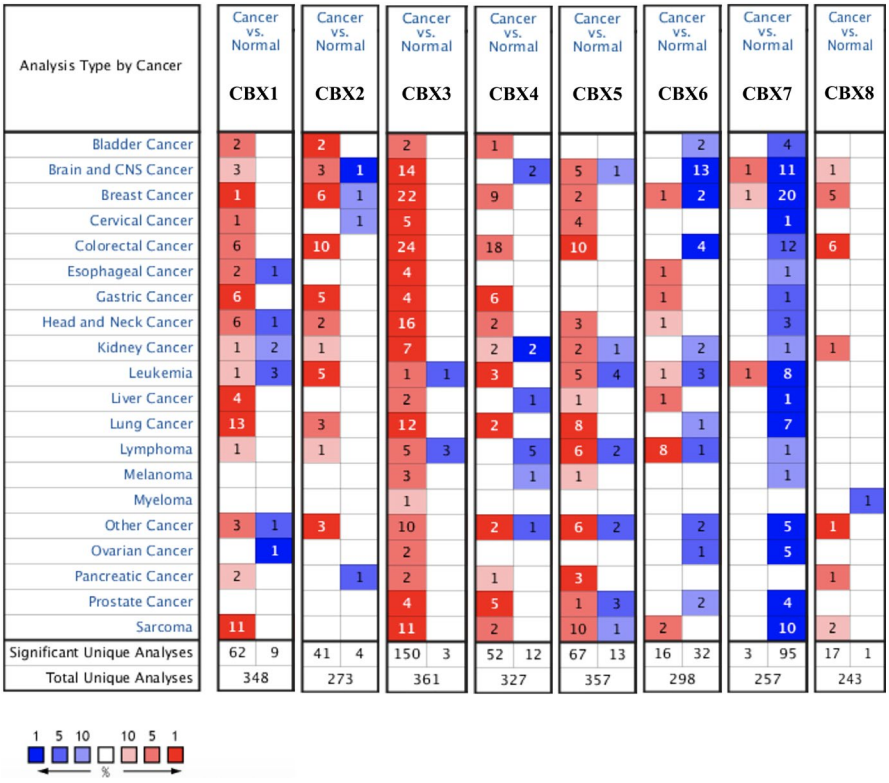


FIGURE 1 CBX family expression level in SKCM (Oncomine). Difference of transcriptional expression was compared by Student's *t* test with *P*-value = .05, fold Change = 1.5, gene rank = 10%, data type: mRNA

TABLE 1 The mRNA levels of CBX family in SKCM (ONCOMINE)

CBXs	Type	Fold change	*P*-value	*t* test	Reference
CBX1	NA	NA	NA	NA	NA
CBX2	NA	NA	NA	NA	NA
CBX3	Skin cutaneous melanoma Skin cutaneous melanoma	3.624 3.768	7.03E-5 2.42E-5	11.380 7.301	PMID:15833814 PMID:16243793
CBX4	NA	NA	NA	NA	NA
CBX5	Skin cutaneous melanoma	1.728	.01	2.600	PMID:18442402
CBX6	NA	NA	NA	NA	NA
CBX7	Skin cutaneous melanoma	−2.400	3.30E-5	−7.515	PMID:16243793
CBX8	NA	NA	NA	NA	NA

module" with a minimum Number of Genes (Size) of 3 and a simulation of 500. The analysis was performed using TCGA_SKCM datasets, and $P < .05$ indicates statistical significance.

3 | RESULTS

3.1 | The expression level of CBX family in the patients with SKCM

We initially explored the expression level of CBX family in SKCM using Oncomine and GEPIA. As a result, the level of CBX3 and CBX5 was upregulated, while the level of CBX7 was significantly downregulated in SKCM tissues compared with normal tissues based on the data of Oncomine (Figure 1, $P < .05$). A total of two datasets suggested that CBX3 was significantly increased in SKCM with a FC of 3.624 and 3.768, respectively (Table 1).[20,21] A gene expression profile revealed that CBX5 was upregulated in SKCM tissue and FC was 1.728 ($P = .01$, Table 1).[22] Downregulation of CBX7 was found in SKCM tissue (FC = −2.400, $P = 3.30E-5$) based on the result of Talantov et al[21]

The results of GEPIA were shown in Figure 2, which indicated significant upregulation of CBX2 (Figure 2B), CBX3 (Figure 2C), and CBX6 (Figure 2F) in tumor tissues in SKCM ($P < .05$). Moreover, the level of CBX7 (Figure 2G) and CBX8 (Figure 2H) was decreased in tumor tissues compared with normal tissues ($P < .05$). We then analyzed the correlation between the level of CBX family and the pathological stage in SKCM. We found that the mRNA expression of CBX1 and CBX2 was significantly associated with the pathological stage in SKCM (Figure 3).

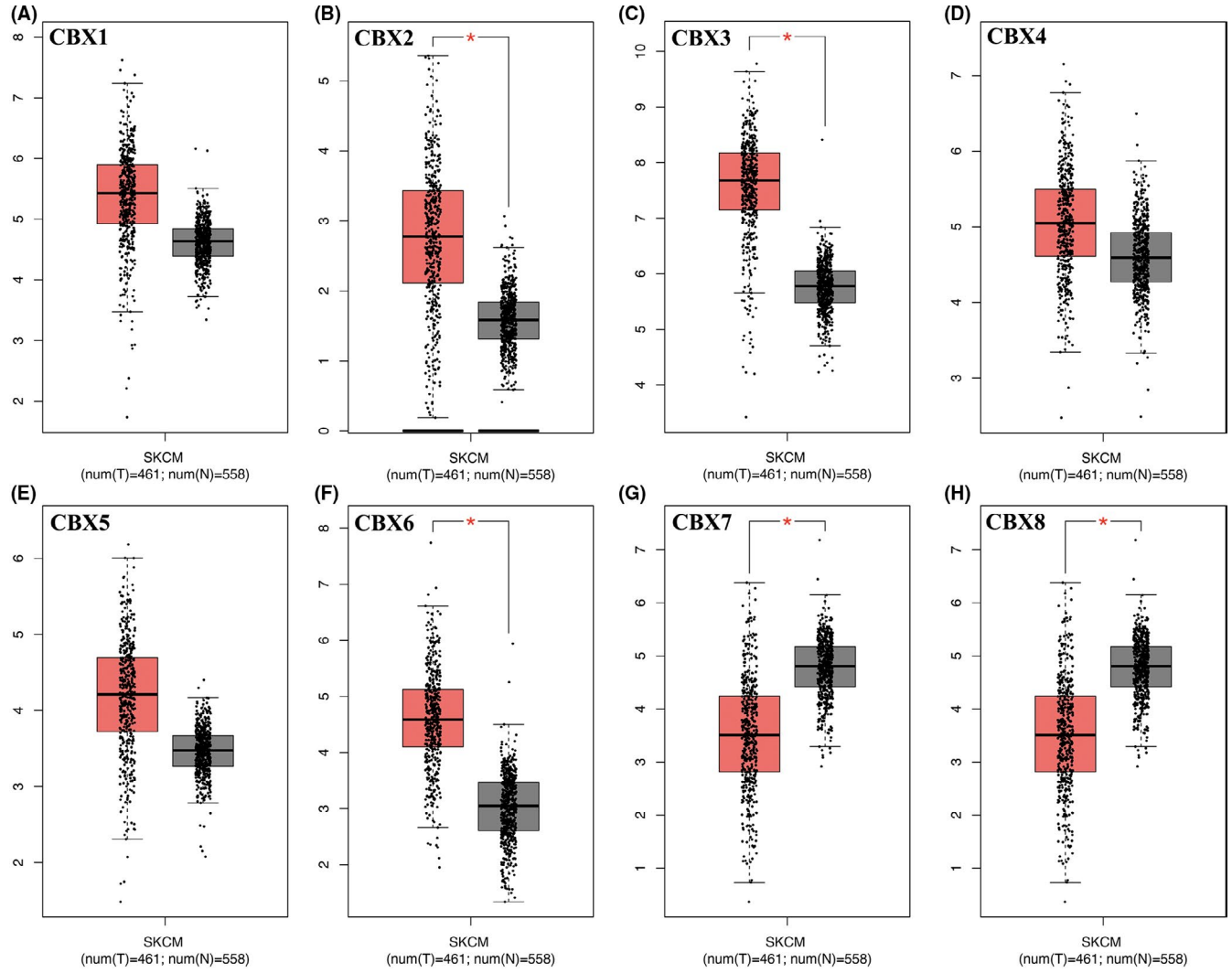


FIGURE 2 The expression of CBX family in SKCM (GEPIA). Box plots derived from gene expression data for GEPIA comparing the expression of a specific CBX family in SKCM with the *P*-value of .05. *Indicate that the results are statistically significant

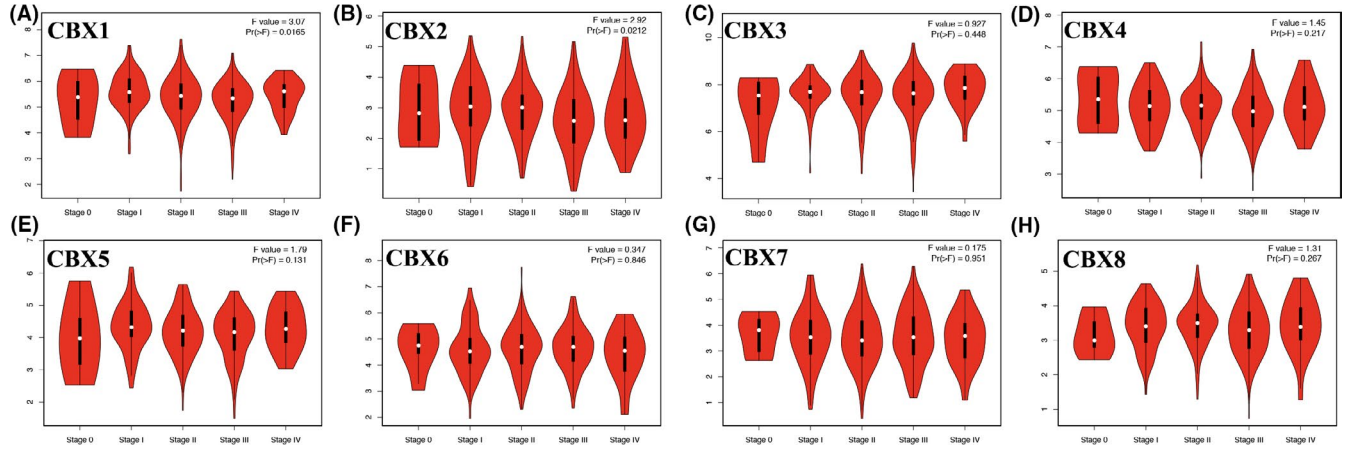


FIGURE 3 Correlation between CBX family expression and pathological stage in SKCM (GEPIA). Violin plot derived from correlation between the expression of a specific CBX family and pathological stage in SKCM with a *P*-value of .05

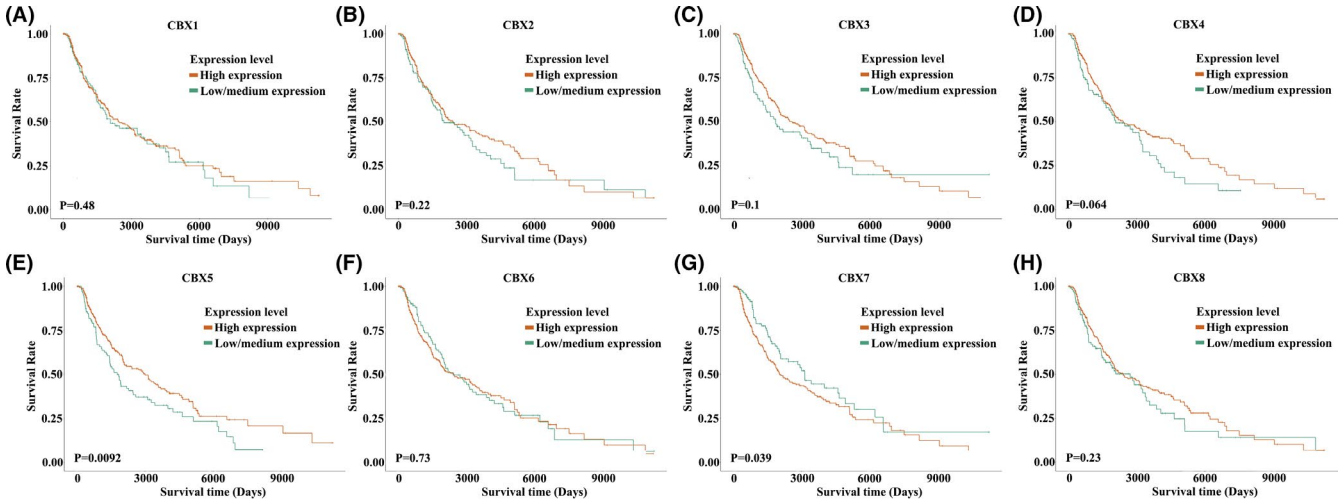
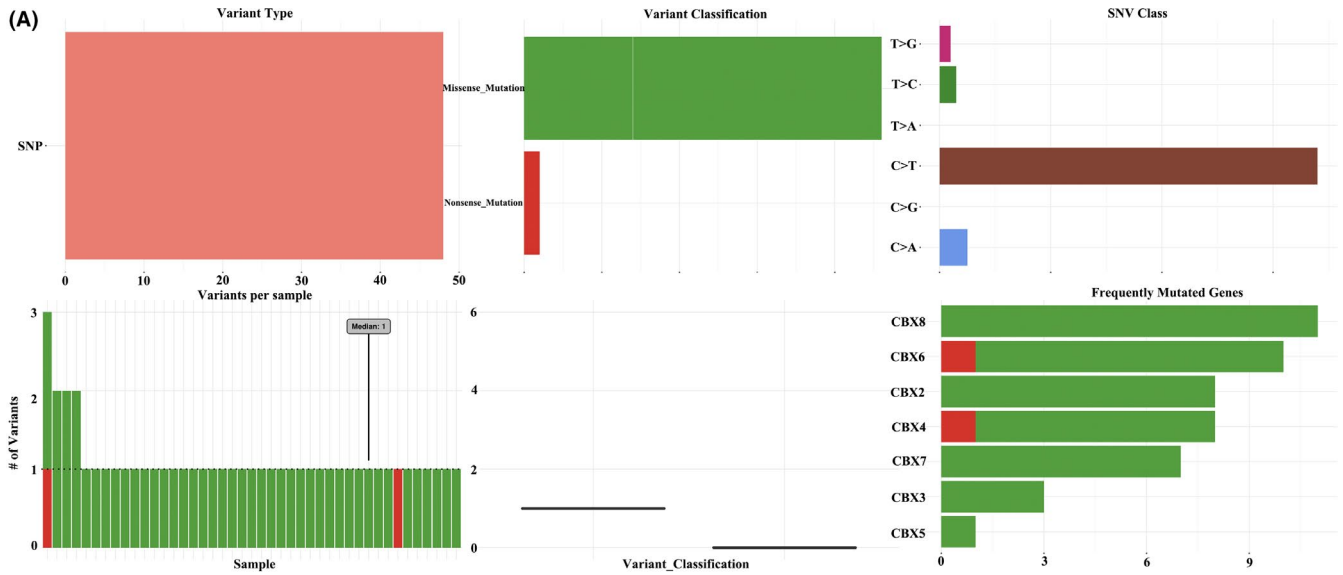


FIGURE 4 The prognostic value of CBX family in SKCM (UALCAN). SKCM patients with high CBX5 level and low CBX7 level had a poor prognosis



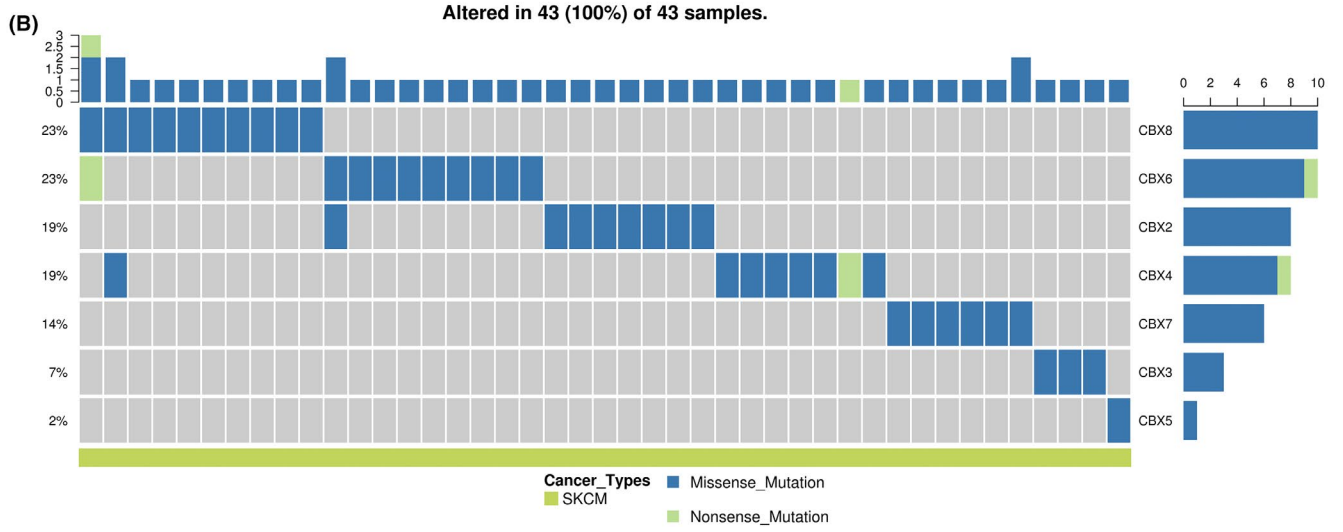


FIGURE 5 The single nucleotide variation (SNV) analysis of CBX family in SKCM (GSCALite). A, summary plot displays SNV frequency and variant types of CBX family in SKCM. B, waterfall plot shows the mutation distribution of CBX family in SKCM and a SNV classification of SNV types

FIGURE 6 Cancer pathway activity and drug sensitivity analysis of CBX family in SKCM (GSCALite). A, The role of CBX family in the famous cancer-related pathways. B, The role of CBX family in the famous cancer related pathways. C, The Spearman correlation represents the gene expression correlates with the drug. The positive correlation means that the gene high expression is resistant to the drug, vise verse

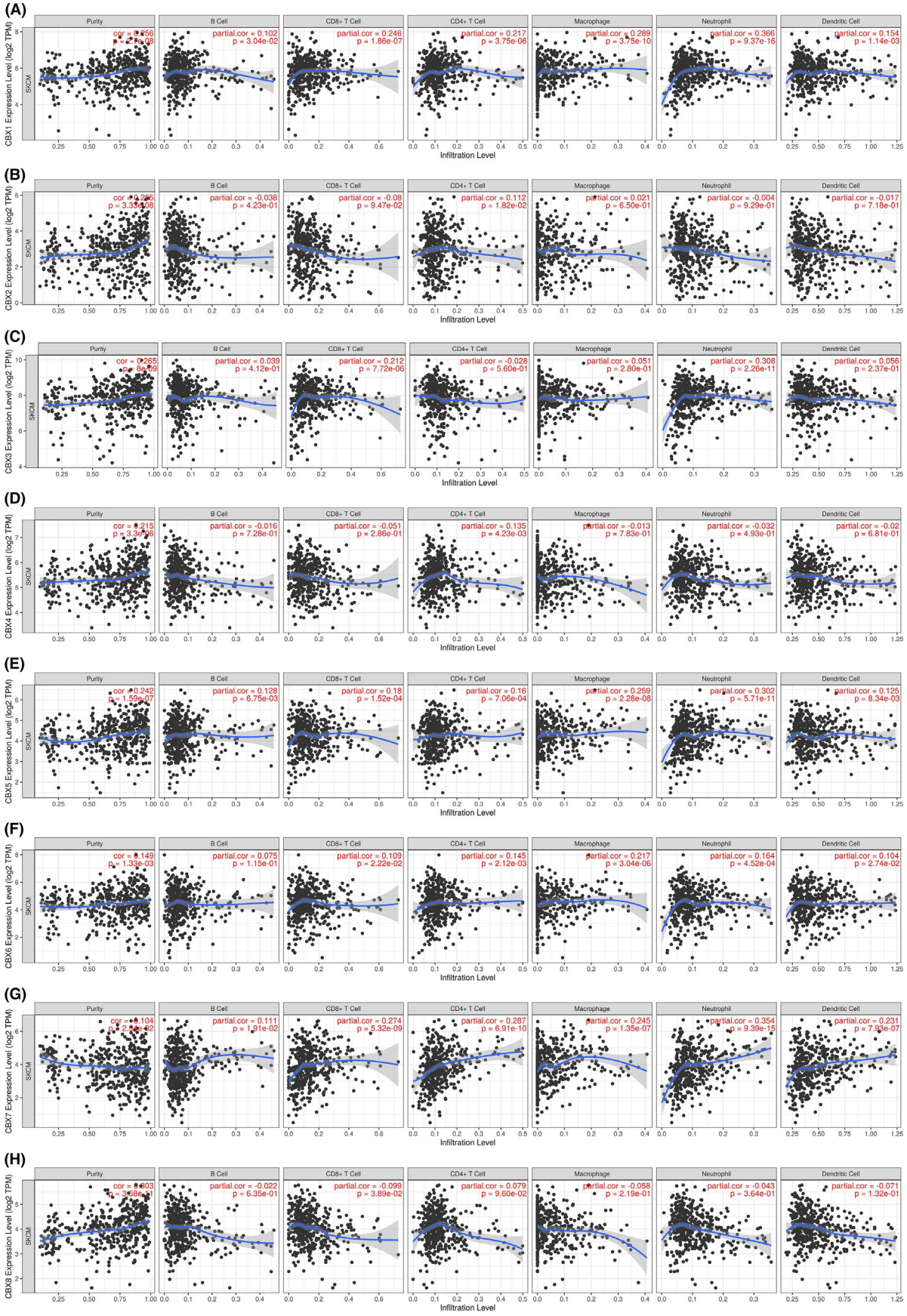


FIGURE 7 Correlation of CBX family expression with immune infiltration level in SKCM (TIMER). The expression of CBX family was certainly positively associated with the infiltration abundance of B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells

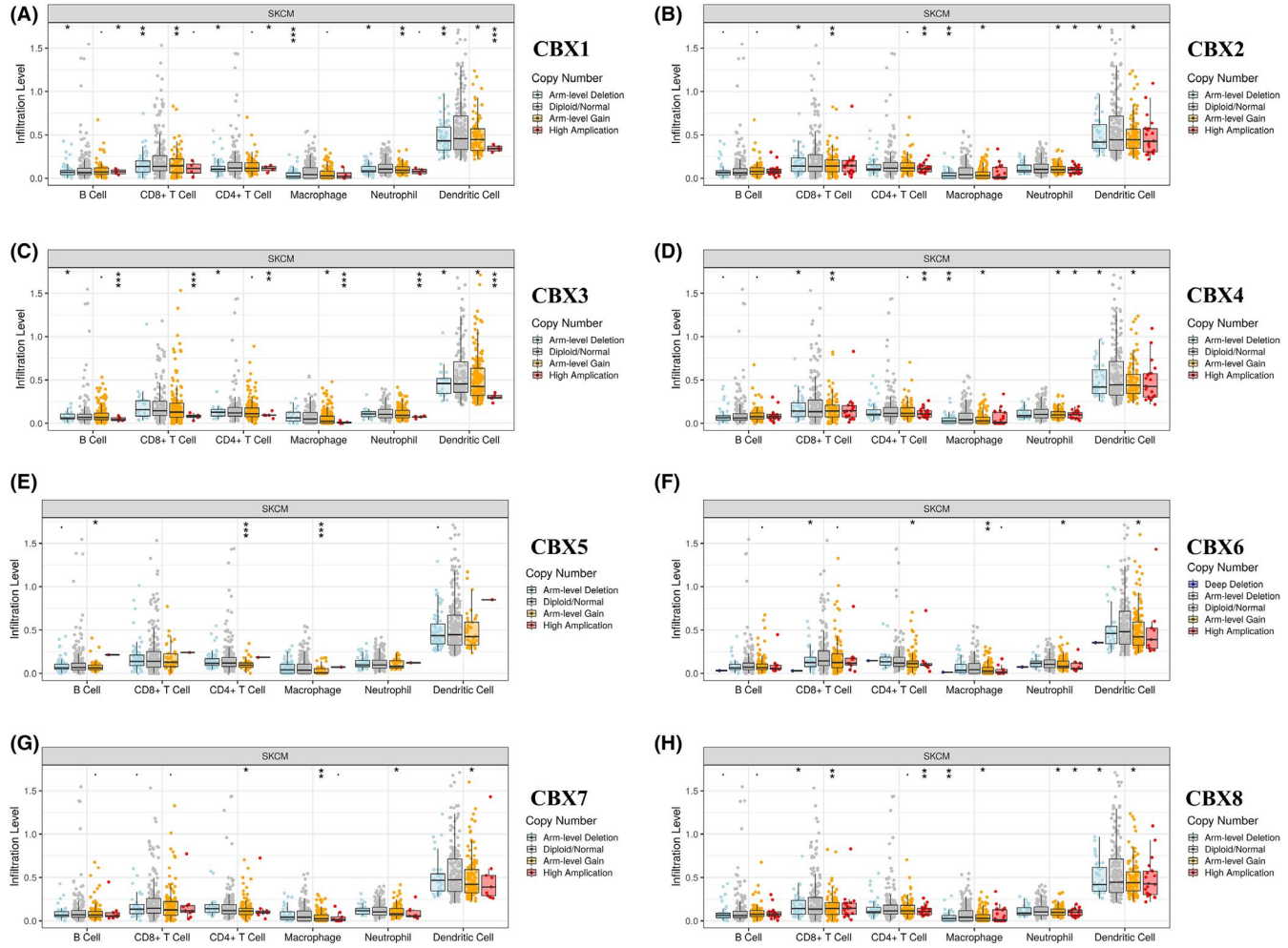


FIGURE 8 The correlation between copy number alteration of IRFs and immune cell infiltration in Glioblastoma

TABLE 2 The top 10 significant genes correlated with CBX family in SKCM (GEPIA)

CBXs	Correlated genes
CBX1	SMARCE1, KHDRBS1, RBMX, DHX40, ZNF286A, SUMO2, COIL, MSL1, KANSL1, SPOP
CBX2	CBX8, MEX3B, MAML1, GLTSCR1, VANGL2, FAM171A2, HNRNPA0, ILF3, BRD3, GPC2
CBX3	CBX3P9, KBTBD2, TAX1BP1, HNRNPA2B1, NUPL2, KLHL7, KRIT1, MRPL32, PSMA2, SNX10
CBX4	CBX8, RPTOR, CSNK1D, KIAA0195, FOXK2, SOX10, EXOC7, NPLOC4, UBE2O, CANT1
CBX5	RBMX, TMPO, SRSF3, RAD21, SRSF1, SENP1, UNC119B, ZNF740, HNRNPU, MATR3
CBX6	DNAL4, SUN2, TOB2, JOSD1, MIEF1, CBX7, TAB1, EP300, MKL1, ZC3H7B
CBX7	SUN2, TRIM56, CBX6, BCL6, EZH1, IGIP, VAMP2, NR3C2, DNAL4, ZBTB4
CBX8	CBX4, CBX2, CSNK1D, KIAA0195, FOXK2, RPTOR, FTSJ3, EXOC7, UBE2O, MAFG

3.2 | The prognostic value of CBX family in the patients with SKCM

We then evaluated the association between CBX family and the prognosis of SKCM patients. And the result suggested that the overall survival of SKCM patients with high CBX5 level was better compared with low/medium CBX5 level (Figure 4E, $P = .0092$), while the overall survival of SKCM patients with high CBX7 level was worse compared with low/medium CBX7 level (Figure 4G, $P = .039$). The other CBX family would not affect the overall survival of SKCM patients. Thus, CBX5 and CBX7 were potential prognostic biomarkers for SKCM.

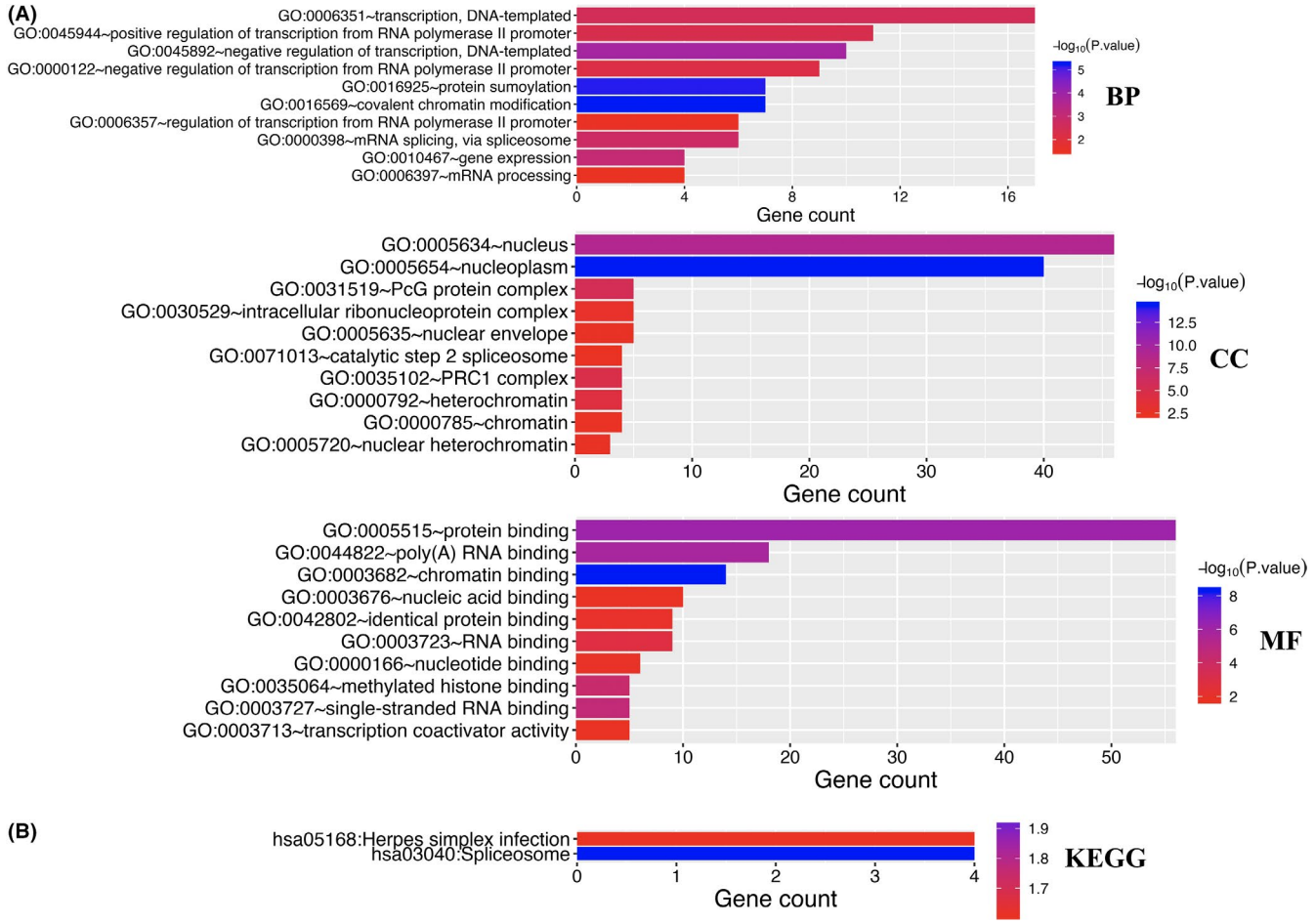


FIGURE 9 Enrichment analysis of CBX family in SKCM (DAVID). A, Cellular components, biological processes, and molecular functions analysis. B, KEGG pathway analysis

3.3 | Genetic alteration, cancer pathway activity, and drug sensitivity analysis of CBX family in SKCM

Having established the survival implications of CBX family, we next explored the role of CBX family in genetic alteration, cancer pathway activity and drug sensitivity in SKCM using GSCALite. Genetic alteration revealed that CBX8 and CBX6 were the top two frequently mutated genes among CBX family (Figure 5). Genetic alteration of CBX family in SKCM were consist of Missense mutation and nonsense mutation (Figure 5). We also analyzed the role of CBX family in famous cancer-related pathways activity, including TSC/mTOR, RTK, RAS/MAPK, PI3K/AKT, Hormone ER, Hormone AR, EMT, DNA Damage Response, Cell Cycle, and Apoptosis pathways. As a result, most member of CBX family were associated with the activation of cell cycle pathway, DNA damage response, and hormone AR pathway. We also found that CBX5/6/7 were mostly associated with the inhibition of apoptosis pathway (Figure 6A). Drug sensitivity revealed that low expression of CBX2 and CBX2 was resistant to certain drugs or small molecules (Figure 6B).

3.4 | Immune infiltrations analysis of CBX family in SKCM

As shown in Figure 7, CBX1 showed significant correlation with the abundance of B cell (cor = 0.102, P = 3.04e-2), CD8+ cell (cor = 0.246, P = 1.86e-7), CD4+ cell (cor = 0.217, P = 3.75e-6), macrophage (cor = 0.289, P = 3.75e-10), neutrophil (cor = 0.366, P = 9.37e-16), and dendritic cell(cor = 0.154, P = 1.14e-3) (Figure 7A). As for CBX2, CBX4, and CBX8, significant correlations were obtained between gene expression and the abundance of CD4+ cell (Figure 7B,D,H). Besides, CBX3 showed significant correlation with the abundance of CD8+ cell (cor = 0.212, P = 7.72e-06) and neutrophil (cor = 0.308, P = 2.26e-11) (Figure 7C). Interestingly, the expression of CBX5 and CBX7 was associated with the abundance of these six immune cells (B cell, CD8 + cell, CD4 + cell, macrophage, neutrophil, and dendritic cell) (Figure 7E,G). Except for B cell, CBX6 was positively correlated with the abundance of the other immune cells (CD8+ cell, CD4+ cell, macrophage, neutrophil, and dendritic cell) (Figure 7F). Moreover, somatic copy number alterations of CBX family could certainly inhibit the immune cell infiltrations in SKCM (Figure 8).

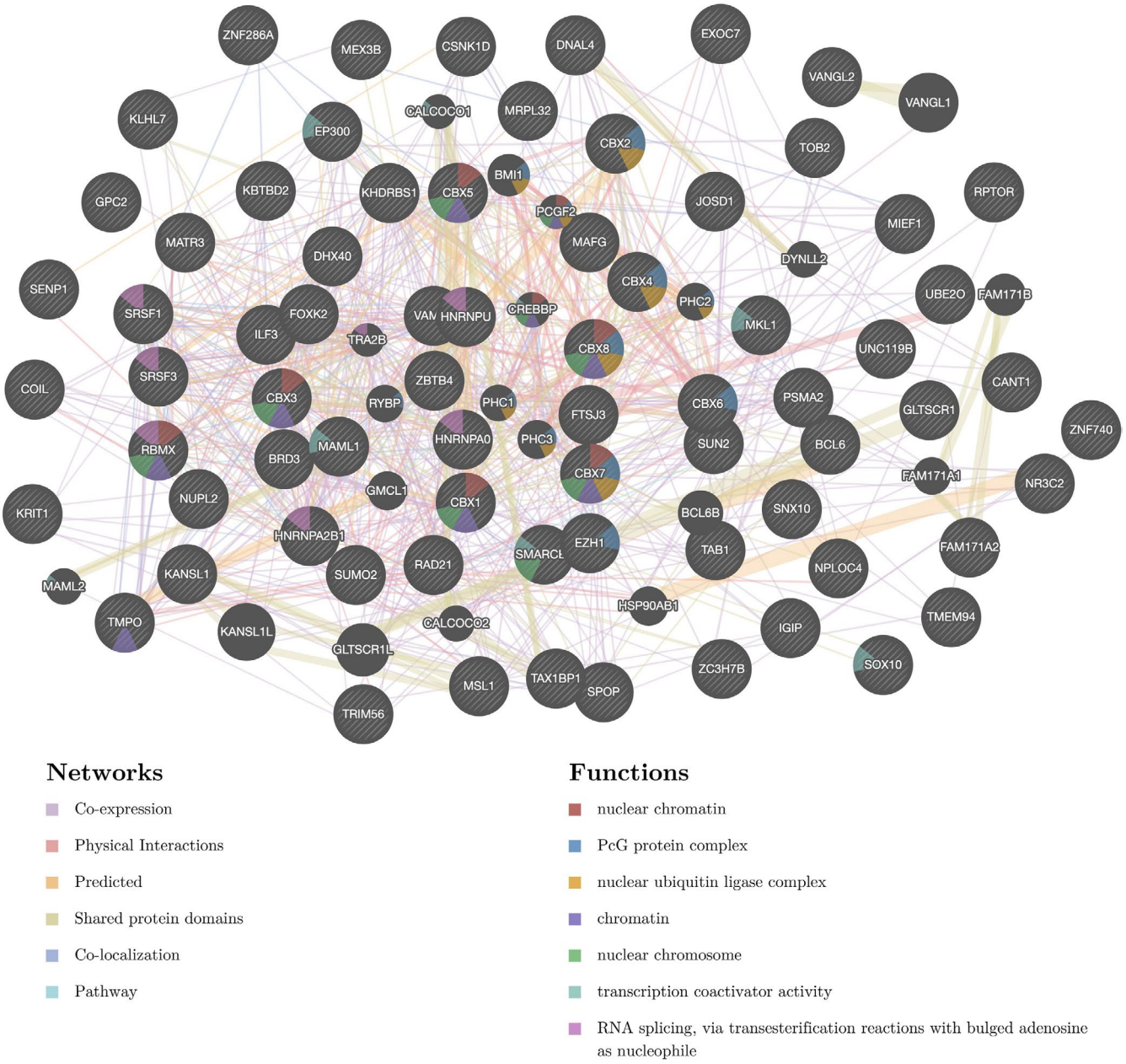


FIGURE 10 PPI network of CBX family (GeneMANIA). Different colors of the network edge indicate the bioinformatics methods applied: co-expression, website prediction, pathway, physical interactions, and co-localization. The different colors for the network nodes indicate the biological functions of the set of enrichment genes

3.5 | Enrichment analyses of CBX family in SKCM

We then performed enrichment analyses of CBX family using DAVID. We first explored the top ten genes correlated with each member of CBX family using GEPIA (Table 2). After that, we submitted CBX family and correlated genes to DAVID for enrichment analyses. Biological process (BP) analysis suggested that CBX family were associated with covalent chromatin modification, protein sumoylation, negative regulation of transcription, and mRNA splicing, via spliceosome (Figure 9A). Cellular component (CC) analysis suggested that CBX family were involved in nucleoplasm, nucleus, PcG protein complex, PRC1 complex, and heterochromatin (Figure 9A). Moreover, molecular function (MF) analysis revealed that CBX family and correlated genes were enriched in chromatin binding, protein binding, poly(A) RNA binding, single-stranded RNA binding, methylated histone binding and RNA binding and transcription coactivator activity (Figure 9A). Result of Kyoto Encyclopedia of Genes and Genomes (KEGG) revealed that CBX family and correlated genes were enriched in herpes simplex infection, and spliceosome (Figure 9B). PPI network was constructed and revealed that CBX family were associated with nuclear chromatin, PcG protein complex, nuclear ubiquitin ligase complex, chromatin, transcription coactivator activity, and RNA splicing (Figure 10).

TABLE 3 The Kinase target networks of CBX family in SKCM (LinkedOmics)

CBXs	Kinase targets	LeadingEdgeNum	*P*-value
CBX1	Kinase_ATM	123	0
	Kinase_PLK1	91	0
CBX2	Kinase_GSK3B	52	0
	Kinase_RPS6KA1	17	0
CBX3	Kinase_PLK1	91	0
	Kinase_ATM	123	0
CBX4	Kinase_Mtor	20	0
	Kinase_MAPK13	14	0
CBX5	Kinase_CDK2	85	.004
	Kinase_CDK1	96	.004
CBX6	Kinase_MAPK1	72	0
	Kinase_MAPK6	9	0
CBX7	Kinase_CDK1	84	0
	Kinase_PLK1	27	0
CBX8	Kinase_ATM	28	0
	Kinase_CDK2	78	0

TABLE 4 The miRNA target networks of CBX family in SKCM (LinkedOmics)

CBXs	miRNA targets	LeadingEdgeNum	*P*-value
CBX1	ATGTTAA, MIR-302C	132	0
	CATGTAA, MIR-496	94	0
CBX2	GGGGCCC, MIR-296	25	0
	CCAGGGG, MIR-331	36	0
CBX3	ATATGCA, MIR-448	75	0
	ATCATGA, MIR-433	54	0
CBX4	CCAGGGG, MIR-331	46	0
	GGGGCCC, MIR-296	41	0
CBX5	CATGTAA, MIR-496	34	0
	GTATTAT, MIR-369-3P	35	0
CBX6	CTATGCA, MIR-153	77	0
	CAGTGTT, MIR-141, MIR-200A	112	0
CBX7	GAGCCTG, MIR-484	26	0
	ATGCTGC, MIR-103, MIR-107	90	.002
CBX8	CCAGGGG, MIR-331	37	0
	GGGGCCC, MIR-296	19	0

3.6 | The kinase and miRNA target networks of CBX family in SKCM

In order to further reveal the potential mechanism of CBX family in SKCM, the kinase and miRNA target analysis of CBX family in SKCM were also explored with LinkedOmics. As shown in Table 3, kinase ATM was suggested as the target of CBX1, CBX3, and CBX8. Moreover, kinase PLK1 was suggested as the target of CBX1, CBX2, and CBX7 (Table 3). Kinase CDK1 was suggested as the target of CBX5/6 (Table 3). The results of miRNA target were shown in Table 4. (CCAGGGG) MIR-331 and (GGGGCCC) MIR-296 were suggested as the miRNA target of CBX2, CBX4, and CBX8. Moreover, (CATGTAA) MIR-496 was suggested as the miRNA target of CBX1 and CBX5.

4 | DISCUSSION

SKCM originating from melanocytes is one of the deadliest diseases.[4] The tumorigenesis of SKCM is a multilevel, multistep, complex process associated with an interaction of exogenous and endogenous events and polygenic variation.[23] Early detection, reasonable therapy, and accurate prediction of prognosis are of great importance for SKCM patients, since the 5-year survival rate of patients with metastatic disease is 15-20%.[24] Thus, these sobering data illustrate a critical need for novel biomarkers related to the prognosis and therapy of SKCM. And our study is performed.

We first focus on the expression and prognosis value of CBX family in SKCM. As a result, the level of CBX2, CBX3, CBX5, and CBX6 was upregulated while the level of CBX7 and CBX8 was downregulated in tumor tissues in SKCM. And prognosis analysis revealed that SKCM patients with high CBX5 level and low CBX7 level had a poor prognosis, demonstrating CBX5 and CBX7 as potential prognosis biomarkers for SKCM. Actually, some of members of CBX family were also suggested as biomarkers for other types of cancer. In hepatocellular carcinoma, CBX1/2/3/6/8 served as prognostic biomarkers for survivals.[10] Another study revealed that CBX4 may act as a biomarker for the prognosis of breast cancer.[25]

Another important finding of the current study was that CBX family and correlated genes were enriched in chromatin modification, PcG protein complex, transcription coactivator activity, protein binding, RNA splicing, cell cycle pathway, DNA damage response, and hormone AR pathway. RNA splicing was a widespread process involved in structural transcript variation and proteome diversity.[26] Abnormal splicing process could result in tumor genesis and progression, including SKCM.[26,27] CBX family as transcriptional repressors recruited to many developmental control genes, could regulate tumor metastasis and proliferation.[28,29] Therefore, CBX family may affect the tumorigenesis and progression of SKCM by regulating RNA splicing and transcription coactivator activity.

Our study also revealed that the expression of CBX family was associated with the abundance of certain immune cells and somatic copy number alterations of CBX family could certainly inhibit the immune cell infiltrations in SKCM. Limited studies were performed to clarified the role of CBX family in immune infiltrations. Jian et al revealed that CD4(+) T cells expressed CBX7 and the latter prevented FasL expression and the activation-induced CD4(+) T-cell apoptosis.[30] Therefore, our result covers a non-traditional function of CBX family and adds new insight into immune cell infiltrations.

Genomic instability and mutagenesis were the initial driving forces of tumorigenesis and development and Kinases could help stabilize and repair genomic DNA.[31] Our study identified several kinase targets of CBX family in SKCM, including PLK1 and CDK1. Interestingly, we found that these kinases were associated with genomic stability, mitosis, and transcription activity.[32,33] Upregulation of PLK1 could maintain chromosomal instability and inhibit the genesis and proliferation of cancers.[33,34] PLK1 alteration could facilitate cancerous transformation and promote cancer development.[35] Therefore, CBX family may regulate SKCM development via PLK1.

It cannot be denied that our study has some limitations. First, our study only discusses changes at the gene level and lacks changes in the protein level. Moreover, it would be better to verify the conclusions with other datasets.

In summary, our results clarified the clinical significance and prognostic value of CBX family in SKCM, uncovering the molecular mechanisms involved in the tumorigenesis and progression of SKCM and providing additional choice for the prognosis and therapy biomarker for SKCM.

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