Original Article

Screening and expression verification of key genes in cutaneous squamous cell carcinoma

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Background: Cutaneous squamous cell carcinoma (cSCC), a common skin malignancy, often occurs at exposed sites, and patients' appearance after surgical resection can be affected. This study sought to screen the key genes of cSCC via a bioinformatics analysis and explore the clinical significance and possible potential mechanisms of these genes in cSCC.

Methods: We screened differentially expressed genes (DEGs) between cSCC and normal skin tissues from the Gene Expression Omnibus database, performed functional enrichment and protein interaction network analyses, and used Cytoscape software to identify the key genes. The expression of the genes was proved by immunohistochemistry.

Results: A total of 164 DEGs were screened, and the functional enrichment analysis showed that the DEGs were significantly enriched in deoxyribonucleic acid replication and the cell-cycle pathway. By constructing a protein-to-protein interaction network, kinesin family member 11 (*KIF11*), aurora kinase A (*AURKA*), minichromosome maintenance complex component 2 (*MCM2*), minichromosome maintenance 10 replication initiation factor (*MCM10*), and denticleless E3 ubiquitin protein ligase homolog (*DTL*) were identified as 5 key genes with the highest connectivity. The expression of *KIF11*, *AURKA*, and *MCM2* were investigated by immunohistochemistry. Compared to the normal skin tissues, the positive rates of the *KIF11* and *MCM2* proteins in the cSCC tissues were 70.0% and 90.0%, respectively, and the difference was statistically significant ($P<0.05$). The positive rates of *AURKA* protein expression in the cSCC and normal skin tissues were 13.9% and 0%, respectively, but the difference was not statistically significant. There was no correlation between the above-mentioned 3 key genes.

Conclusions: *KIF11* and *MCM2* were highly expressed in cSCC, and may be involved in tumorigenesis, and represent novel targets for the clinical diagnosis and treatment of cSCC.

Keywords: Cutaneous squamous cell carcinoma (cSCC); bioinformatics; immunohistochemistry; kinesin family member 11 (*KIF11*); minichromosome maintenance complex component 2 (*MCM2*)

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Introduction

Cutaneous squamous cell carcinoma (cSCC), originating from epidermal or adnexal keratinocytes, is one of the most common skin malignancies in Caucasians, accounting for about 20% of skin cancers (1,2). There are approximately 1 million cases of sSCC annually in the United States, and the lifetime risk of developing this carcinoma in Caucasians is estimated to be 7–11% (3). Blacks are 20% more likely to develop cSCC than basal cell carcinoma (BCC), and the cSCC is more common in the face and lower extremities (4). Among non-melanotic skin tumors in China, the incidence of cSCC is 29.4%, which is slightly higher than that of BCC. The incidence of cSCC continues to rise as population aging increases (5). Since cSCC skin lesions usually occur at exposed sites, scars or defects formed after surgical excision can easily affect patients' appearance, which in turn can seriously affect their health and self-confidence. The prognosis of patients with cSCC after surgical resection is generally good, but some patients are still prone to tumor recurrence or metastasis, which eventually leads to death (6).

With the rapid development of disciplines and technologies in recent years, such as molecular medicine, sequencing, proteomics, and bioinformatics, researchers have discovered that some genes are mutated or abnormally expressed in cSCC. However, as yet, no definite biomarkers have been identified that can be used to predict the aggressiveness, recurrence risk, or poor prognosis of primary cSCC, and more genes need to be further explored and verified by clinical research. This study sought to identify the essential genes of cSCC by bioinformatics and explore their expression in cSCC and normal skin tissues using immunohistochemistry to provide biological targets for further research on the pathogenesis and treatment of cSCC, among which, kinesin family member 11 (*KIF11*) and aurora kinase A (*AURKA*) were the first time to research in cSCC. We present the following article in accordance with the MDAR and STARD reporting checklists (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1267/rc).

Methods

Screening of differentially expressed genes (DEGs)

We obtained 2 data sets from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/gds/). The GSE98780 data set included 45 cases of SCC and 9 cases of normal skin tissue, and the GSE66359 data set included 8 cases of SCC and 5 cases of normal skin tissue. The data were integrated, analyzed, and downloaded using GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/). Probe sets without gene symbols were removed, while gene symbols with multiple probe sets were retained as unique values. The DEGs were defined with a corrected P value <0.05 and a |log fold change| ≥1 and plotted in corresponding volcano and Venn diagrams.

Functional enrichment analyses of DEGs

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) signaling pathway analyses were performed on the DEGs using the Database for Annotation, Visualization, and Integrated Discovery (DAVID; https://david.ncifcrf.gov/). The GO analysis covered biological processes (BPs), cellular components (CCs), and molecular functions (MFs). A P value <0.05 was considered statistically significant.

Selection of key genes

Using the online Search Tool for the Retrieval of Interacting Genes/Proteins (STRING; http://string-db.org/) database, a protein-to-protein interaction (PPI) network of the DEGs was analyzed and built with the DEGs that had the lowest confidence scores (scores >0.7 were considered statistically significant). The interaction core module with the highest MCODE score was obtained using the MCODE plugin in Cytoscape software (http://cytoscape.org/). The first 5 nodes were regarded as the key genes according to the degree value using the cytoHubba plugin in Cytoscape, and they were subjected to functional enrichment analysis by DAVID.

Tissue specimens

A total of 30 cSCC and 16 normal skin tissue paraffin specimens were collected from the Pathology Department of Guangdong Second Provincial General Hospital from January 2015 to September 2021. Among the cSCC cases, there were 16 males and 14 females, ranging in age from 24 to 90 years old, with an average age of (68.43±15.29) years. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Our study was approved by the Ethics Committee of Guangdong Second Provincial General Hospital (No. 2021-KZ-211-02),

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and informed consent was obtained from all the patients.

Immunohistochemistry

Some key genes were selected for the immunohistochemical analysis. The rabbit monoclonal antibodies, anti-kinesin family member 11 (*KIF11*; EPR 23276-52), rabbit anti-Aurora kinase A (*AURKA*; EP1008Y), and rabbit anti-minichromosome maintenance complex component 2 (*MCM2*; EPR 4120), which were purchased from Guangzhou Baben Co., China, were diluted to 1:200.

All the paraffin specimens were serially sectioned to a thickness of 3 μm and heated in an incubator at 60 ℃ for 2 h. The paraffin sections were sequentially subjected to xylene dewaxing, hydration treatment, and antigen retrieval. Endogenous peroxidase was blocked with 3% hydrogen peroxide after the antigen retrieval solution had cooled naturally. Primary antibodies were incubated in a refrigerator at 4 ℃ for >12 h. The secondary antibodies were then incubated in an incubator at 37 ℃ for 30 min. A freshly prepared diaminobenzidine (DAB) staining solution (cat. no. K8002; Dako) was added dropwise for 3 min. The slices were re-dyed with hematoxylin for 1 min, differentiated with 1% hydrochloric acid alcohol for 8 s, and returned to blue in flowing water. After dehydration and sealing, the samples were imaged using optical microscopy (Mshot ML31-M; Guangzhou Mingmei Co., Ltd.) (magnification, ×400).

Result judgment criteria

Under the microscope, cells stained with pale yellow, brownish-yellow, or tan granular material was positive. The results were based on the number and staining intensity of the positive cells. In this study, 5 high-power fields were randomly selected for each specimen. A total of 100 cells were observed per high-power field and scored as a percentage of the positive cells. The number of positive cells was <5% at 0 points, 5–25% at 1 point, 26–50% at 2 points, 51–75% at 3 points, and >75% at 4 points; based on the intensity of the staining, no staining was scored as 0 points; pale yellow as 1 point; brown as 2 points; and tan as 3 points. We multiplied the 2 score results and classified <4 as negative and ≥4 as positive.

Statistical method

SPSS software (version 21.0) was used for the statistical analysis. Comparisons between groups were evaluated by the chi-square test or Fisher's exact test, while the correlation of gene expression was assessed using the Spearman rank correlation analysis. A P value <0.05 was considered statistically significant.

Results

Screening of differentially expressed genes (DEGs)

In this study, 1,942 upregulated DEGs and 2,028 downregulated DEGs were screened from the GSE98780 data set, and 506 upregulated and 351 downregulated DEGs were screened from the GSE66359 data set. A total of 164 DEGs (108 upregulated and 56 downregulated) were obtained from the intersection of the 2 data sets (*Figure 1*).

The results of the functional enrichment analysis

A functional enrichment analysis was performed on the 164 DEGs using the DAVID. The 10 most significantly enriched items in each study were imaged and observed to be visibly different (P<0.05; see *Figure 1C*). The GO analysis showed that the main enriched BPs were deoxyribonucleic acid (DNA) replication and initiation and the G1/S transition of the mitotic cell cycle. The main enriched CCs were the chromosomal centromeric and telomeric regions of the nuclear chromosomal and MCM complexes. The main enriched MFs were DNA helicase activity, adenosine triphosphatase (ATPase) activity, chromatin binding, and histone binding. The KEGG analysis revealed that the DEGs mainly functioned in DNA replication and the cell-cycle pathway.

Access to key genes

The PPI network analysis of the DEGs by STRING yielded 163 nodes and 305 edges (*Figure 2A*). The MCODE plugin selected the highest scoring module (15.412) with 18 nodes and 131 edges (*Figure 2B*). Using the cytoHubba plugin, we identified the following 5 essential genes with the highest degree value: *KIF11*, *AURKA*, *MCM2*, *MCM10*, and *DTL* (*Table 1*). The functional enrichment analysis showed that the above 5 key genes mainly functioned in DNA replication and cell cycle pathways, affecting the separation of mitotic centrosomes and ATPase activity (*Figure 2C*).

Expression of key genes in different tissues

We selected *KIF11*, *AURKA*, and *MCM2* from the 5 key

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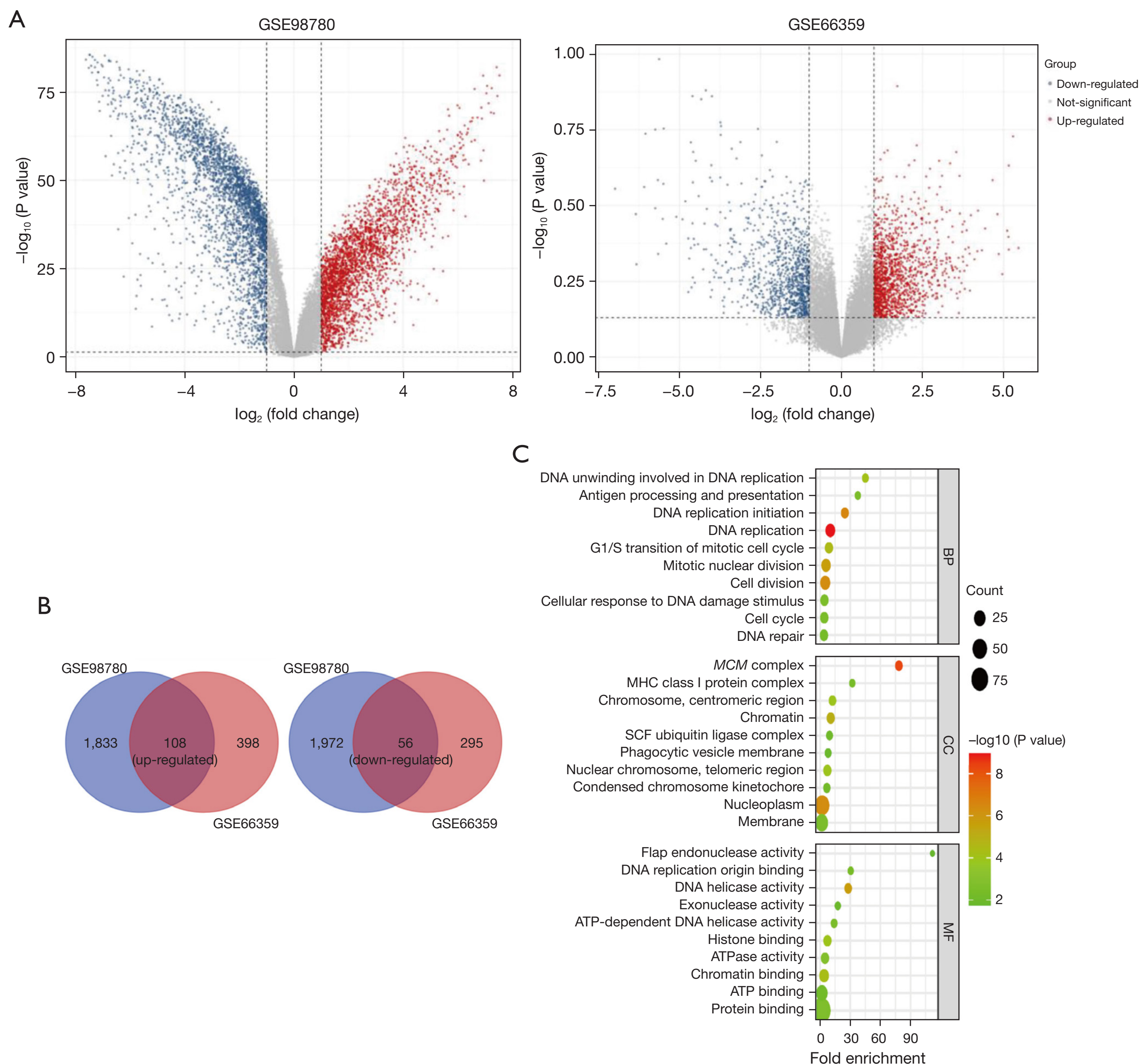

Figure 1 Screening and functional analysis of DEGs. (A) The volcano plots of the GSE98780 and GSE66359 data sets; (B) the Venn diagrams of the 108 upregulated and 56 downregulated DEGs; (C) the GO analysis of the 164 DEGs, including the BPs, CCs, and MFs. DEGs, differentially expressed genes; GO, Gene Ontology; BPs, biological processes; CCs, cellular components; MFs, molecular functions.

genes for immunohistochemical staining (see *Figure 3*). The positive rates of *KIF11* and *MCM2* expression in the cSCC tissues were 70.0% (21/30) and 90.0% (27/30), respectively, while those in normal skin tissues were 18.8% (3/16) and 56.3% (9/16), respectively. The differences between the 2 groups were statistically significant (P<0.05). The positive rates of *AURKA* in cSCC and normal skin tissues were 13.3% (4/30) and 0% (0/16), respectively, but the difference was not statistically significant (see *Figure 3D*).

The association of the key genes in cSCC with clinicopathological features

As *Table 2* shows, the expression levels of the 3 critical genes

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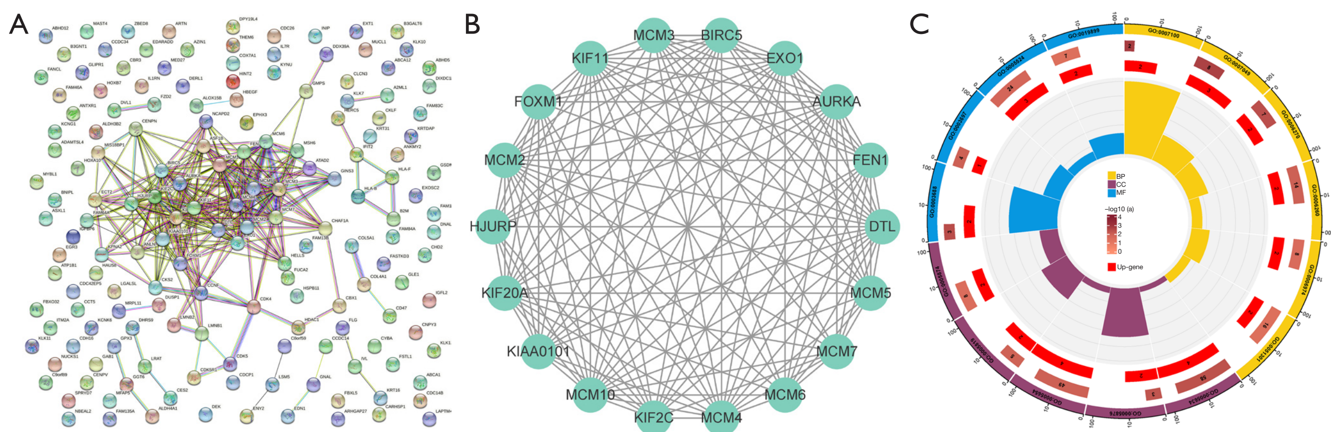

Figure 2 Acquisition of key genes and their expression in sample tissues. (A) A total of 164 DEGs were displayed via the PPI network; (B) the template with the highest score, chosen by Cytoscape software, contained 18 upregulated DEGs; (C) the functional enrichment analysis of the genes *KIF11*, *AURKA*, *MCM2*, *MCM10* and *DTL*. DEGs, differentially expressed genes; PPI, protein-to-protein interaction; *KIF11*, kinesin family member 11; *AURKA*, aurora kinase A; *MCM2*, minichromosome maintenance complex component 2; *MCM10*, minichromosome maintenance 10 replication initiation factor; *DTL*, denticleless E3 ubiquitin protein ligase homolog; BP, biological process; CC, cellular component; MF, molecular function.

Table 1 Top 5 key genes and their interacted nodes

Gene symbol	Gene name	Score (degree)
KIF11	Kinesin family member 11	17
AURKA	Aurora kinase A	17
MCM2	Minichromosome maintenance complex component 2	17
MCM10	Minichromosome maintenance 10 replication initiation factor	17
DTL	Denticleless E3 ubiquitin protein ligase homolog	17

were not related to differences in the patients' gender, age, tumor location, size, differentiation grade, tumor depth, perineural, or lymphovascular invasion.

The correlation analysis of the key genes in cSCC

There were no significant correlations between the positive manifestations of *KIF11*, *AURKA*, and *MCM2* in the 30 SCC cases (P>0.05; see *Figure 4*).

Discussion

In this study, the 5 genes most likely related to the pathogenesis of cSCC tumors were screened from public databases. A functional enrichment analysis revealed that the DEGs mainly acted on cell chromosomes, including the centromeric and telomeric regions. The DEGs participated in DNA replication and the cell cycle by regulating DNA replication origin binding, DNA helicase activity, histone binding, and ATPase activity, which affected the transmission of genetic materials and gradually led to the occurrence and development of the tumor. CSCC is characterized by a high frequency of chromosomal mutations and genomic instability, which may be related to biological changes in telomeres (7). Regular cell-cycle regulation in tumors can be interrupted in various ways, and abnormal DNA replication in the cell cycle is one of the reasons for cancer cell formation (8).

KIF11, *AURKA*, and *MCM2* were examined by immunohistochemistry in our study. Compared to the normal skin tissues, the staining scores of the *KIF11* and *MCM2* proteins were significantly increased in the

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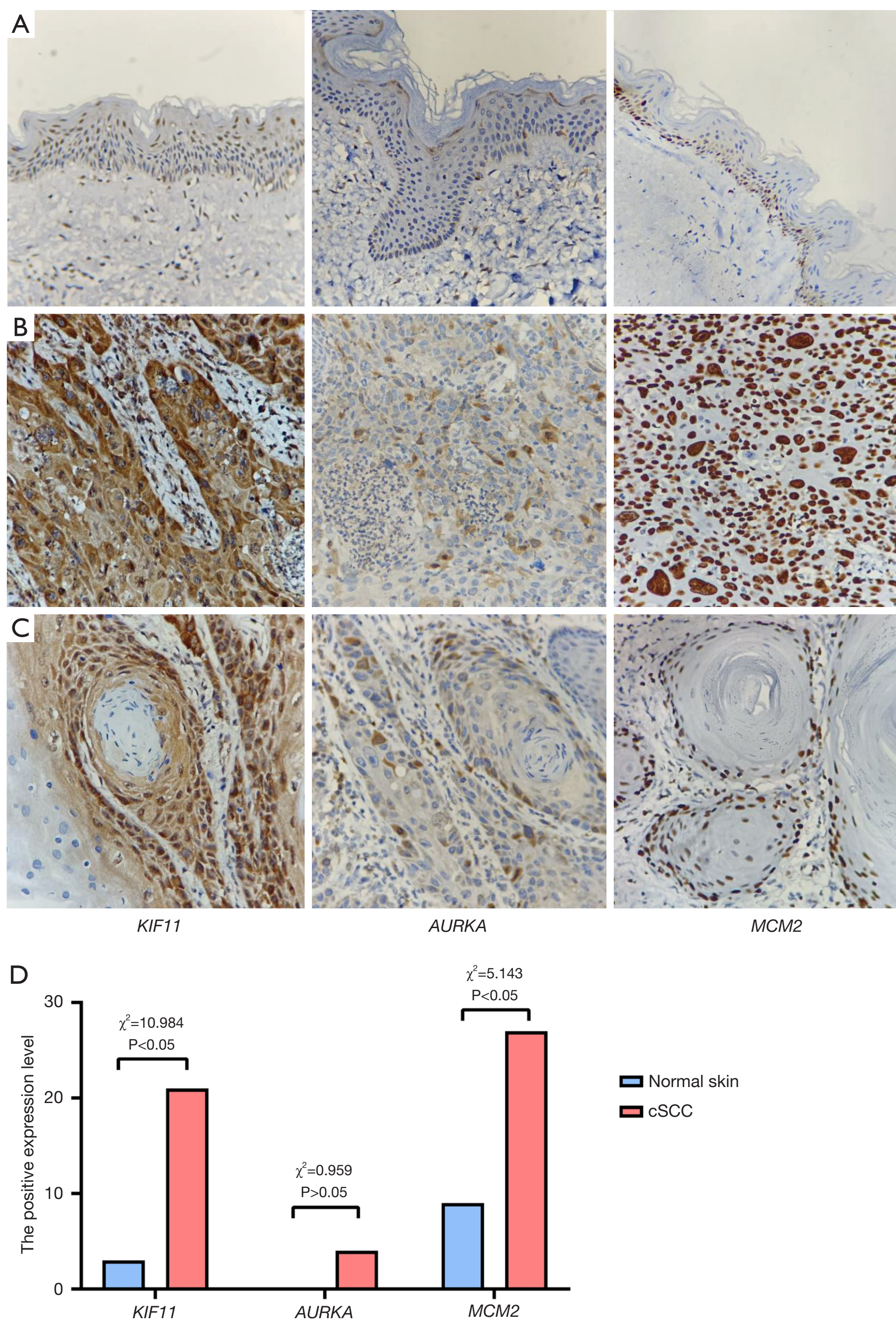

Figure 3 The expression of *KIF11*, *AURKA*, and *MCM2* proteins. Normal skin tissue (A), moderately or poorly differentiated cSCC (B), and well-differentiated cSCC (C) were immunohistochemically stained with rabbit anti-*KIF11*, rabbit anti-*AURKA*, and rabbit anti-*MCM2* antibodies, respectively (×400). (D) the positive expression levels of *KIF11*, *AURKA*, and *MCM2* in different tissues. *KIF11*, kinesin family member 11; *AURKA*, aurora kinase A; *MCM2*, minichromosome maintenance complex component 2; cSCC, cutaneous squamous cell carcinoma.

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Table 2 The expressions of *KIF11*, *AURKA*, and *MCM2* of cSCC patients in relation to different clinicopathological features

Clinicopathological features	Cases	*KIF11*		*AURKA*		*MCM2*	
		Positive, n (%)	P value	Positive, n (%)	P value	Positive, n (%)	P value
Gender			0.694		0.602		0.586
Male	16	12 (75.0)		3 (18.8)		15 (93.8)	
Female	14	9 (64.3)		1 (7.1)		12 (85.7)	
Age (years)			0.427		1.000		1.000
<70	15	9 (60.0)		2 (13.3)		13 (86.7)	
≥70	15	12 (80.0)		2 (13.3)		14 (93.3)	
Tumor location			1.000		1.000		0.548
Exposed*	12	8 (66.7)		1 (9.1)		10 (83.3)	
Non-exposed**	18	13 (72.2)		3 (15.8)		17 (94.4)	
Size (cm)			0.236		0.602		0.090
<2	16	13 (81.3)		3 (18.8)		16 (100.0)	
≥2	14	8 (57.1)		1 (7.1)		11 (78.6)	
Grade			1.000		0.113		0.565
Moderately or poorly differentiated	17	12 (70.6)		4 (23.5)		16 (94.1)	
Well-differentiated	13	9 (69.2)		0 (0.0)		11 (84.6)	
Tumor depth			0.675		0.584		0.532
Shallow	20	13 (65.0)		2 (10.0)		17 (85.0)	
Deep	10	8 (80.0)		2 (20.0)		10 (100.0)	
Perineural and lymphovascular invasion			0.393		0.548		1.000
Yes	7	6 (85.7)		0 (0.0)		7 (100.0)	
No	23	15 (65.2)		4 (17.4)		20 (87.0)	

*, including head, neck, face, and back of the hand; **, including trunk, external genitalia, and limbs (except back of the hand). *KIF11*, kinesin family member 11; *AURKA*, aurora kinase A; *MCM2*, minichromosome maintenance complex component 2; cSCC, cutaneous squamous cell carcinoma.

cSCC tissues. Additionally, *AURKA* was only significantly expressed in the cSCC samples from individual cases, and the difference was not statistically significant. The *KIF11* and *MCM2* proteins were mainly expressed in the basal layer cells of the normal skin. The expression and distribution of these 3 genes were similar in cSCC. Specifically, they were widely or diffusely distributed in moderately or poorly differentiated tumors and were mainly distributed around keratinocytes in well-differentiated tumors, which may be related to the level of tumor cell proliferation and differentiation.

The *KIFs*, comprises 14 families (i.e., kinesin 1–14A/B) of highly conserved motor proteins that are involved in chromosomes and spindles during mitosis and meiosis movement (9). *KIF11* acts in early mitosis, and its inactivation can cause mitotic arrest in the cell cycle, leading to cell death (10). Its overexpression generates additional driving forces during mitosis, leading to the premature division of sister chromatids and uneven chromosomal distribution, which causes aneuploidy in daughter cells and may result in tumorigenesis (11). The overexpression of *KIF11* in laryngeal squamous cell carcinoma is associated with lymph node metastasis, tumor stage, and poor prognosis (12). *KIF11* regulates the occurrence

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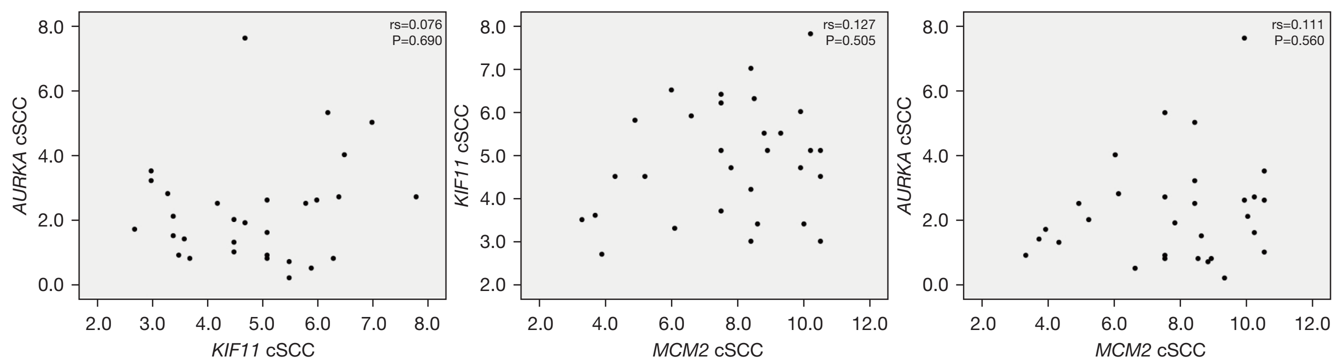

Figure 4 Genes correlations. A Spearman's rank correlation analysis was conducted to detect the correlation between the expression of *KIF11*, *AURKA*, and *MCM2* in cSCC. *KIF11*, kinesin family member 11; *AURKA*, aurora kinase A; *MCM2*, minichromosome maintenance complex component 2; cSCC, cutaneous squamous cell carcinoma; rs, spearman correlation coefficient.

mechanism of breast cancer and is highly expressed in well-differentiated and malignant tumor cells, affecting patient prognosis (13). This study found, for the first time, that *KIF11* protein was abnormally highly expressed in cSCC, indicating that *KIF11* is closely related to the pathogenesis of cSCC. As a kinesin inhibitory active molecule of *KIF11*, K858 has significant antitumor activity. K858 inhibits cell replication by disrupting the normal structure of the spindle during cell mitosis, blocks the cell cycle in G2 phase, and induces apoptosis (14). *KIF11* affects the progression of various tumors, and its high expression is correlated with patient prognosis; thus, it could be a potential therapeutic target in cSCC (9).

The family of minichromosome maintenance proteins (*MCMps*) is a major regulator of DNA replication, is involved in DNA replication and cell-cycle regulation, and is a specific indicator of cell proliferation (15). The hexameric complex formed by *MCM2*–7, as the core component of the eukaryotic helicase, plays a vital role in the origin and elongation of DNA replication (16). In the *MCM* complex, the helicase activity is mainly mediated by trimeric complexes formed by *MCM4*, *MCM6*, and *MCM7*. *MCM2* can adhere to the trimeric complex to prevent its assembly and inhibit helicase activity (17). As a critical factor in the occurrence and development of cSCC, *MCM2* promotes cell proliferation mainly in the basal layer of the epidermis, proliferative skin lesions, and malignant skin tumors (18). Tachibana *et al.* confirmed that the cellular expression level of *MCM2* affects the severity of cell variation and can be used as a specific marker of cell proliferation (19).

In normal squamous epithelial cells, *MCM*-positive cells are present in areas of basal cell hyperplasia but not in superficially differentiated keratinocytes. The expression distribution of *MCM2* in different differentiated cSCCs was characteristic. *MCM2*-positive expression is peripherally distributed in well-differentiated squamous cell carcinomas and diffusely distributed in poorly differentiated squamous cell carcinomas (8). Our study suggests that the positive rate of *MCM2* expression in cSCC is as high as 90%. *MCM2* can be used to distinguish between normal and tumor tissues with widespread and characteristic staining. Hsieh *et al.* found that the small molecule BI-2536, as a polo-like kinase 1 (PLK-1) inhibitor, reduced the expression levels of *MCM2* in neuroblastoma cells, promoted mitochondrial fusion, G2/M arrest, and resulted in cellular apoptosis (20). Therefore, *MCM2* could be used as an essential indicator for the early diagnosis of cSCC and a research target for treatment.

AURKA is a crucial regulator of cytokinesis, and its overexpression can cause centrosome amplification and abnormalities in spindle formation, resulting in tumor cell aneuploidy and chromosomal instability (21). It is a research target for the treatment of head and neck squamous cell carcinoma (HNSCC) through the signaling pathway of *AURKA*/Akt/focal adhesion kinase (FAK), which activates FAK and promotes the migration and invasion of HNSCC cells (22). Increased *AURKA* expression shortens the lifespan of pancreatic cancer patients. The *AURKA* inhibitor CCT137690 was shown to induce orthotopic and subcutaneous tumor cell necrosis and immunogenic cell death in mouse pancreatic cancer, thus slowing tumor growth (23). Apart from Davis (24), who reported that the TAp63-miR-30c-2*/miR-497-*AURKA* axis could serve as a therapeutic target in cSCC, little research has

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been conducted on *AURKA* in cSCC. Our study showed that compared to natural skin tissues, the expression of *AURKA* in cSCC tissues is not obvious, and only a few cases showed sporadic expression, suggesting that the expression mechanism of *AURKA* in different tumors or tumors of various origins may vary. The skin is the largest organ of the human body, and the mechanism of *AURKA* in skin tumors may differ to that in other tumors. However, inconsistent with our immunohistochemical results, the previous online database analysis showed that *AURKA* was significantly differentially expressed in cSCC tumor tissues compared to normal tissues. The above conclusions do not rule out the limitations of the samples studied in our experiment, or that the *AURKA* gene affected the oncogenic mechanism in cSCC through other pathways, which remains to be further verified.

No significant correlations were observed between the expression of *KIF11*, *AURKA*, and *MCM2* in the cSCC and normal skin tissues. These 3 genes might exert their respective effects through more complex regulatory mechanisms, thus affecting the occurrence and development of skin tumors; however, this needs to be further explored.

In summary, the bioinformatic analysis revealed that 5 key genes may play crucial roles in the pathogenesis of cSCC. Among them, verified by clinical data, *KIF11* and *MCM2* were specifically highly expressed in cSCC, which may be involved in tumorigenesis and provide novel targets for the clinical diagnosis and treatment of cSCC.

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Footnote

Reporting Checklist: The authors have completed the MDAR and STARD reporting checklists. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1267/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1267/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1267/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Guangdong Second Provincial General Hospital (No. 2021-KZ-211-02). Informed consent was taken from all the patients.

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