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Key cell cycle genes in cervical cancer and their potential role in neuromuscular complications: a bioinformatics perspective

Xiaojing Liu, Jialiang Sun, Huijuan Qi, Lina Dong

Department of Gynecology, Affiliated Hospital of Chifeng University, Chifeng City, China.

Abstract

This study aimed to identify key cell cycle–related genes involved in cervical cancer progression using comprehensive bioinformatics analyses and to explore their potential implications in neuromuscular complications associated with cancer pathology or treatment. Gene expression profiles related to cervical cancer (GSE63514, GSE6791, GSE52903, and GSE9750) were retrieved from the GEO database. Differentially Expressed Genes (DEGs) distinguishing tumour tissues from normal tissues were determined through Venn diagram analysis. Functional enrichment was conducted via Gene Ontology (GO) and KEGG pathway analyses. A Protein-Protein Interaction (PPI) network was constructed using the STRING database, and core hub genes were screened through Cytoscape. Validation of selected genes was performed using GEPIA. A total of 117 DEGs were identified, with 89 upregulated and 28 downregulated genes. In this case, five hub genes—CDK1, CCNA2, CDC20, TOP2A, and EXO1—displayed significant overexpression in cervical cancer tissues with p values lower than 0.05. It is noteworthy that CCNA2 was associated with increased tumour stage and worse Disease-Free Survival (DFS), and CDK1 with worse Overall Survival (OS). These genes play crucial roles in the regulatory circuits of the cell cycle, and their altered expression may impact a range of cellular processes beyond cancer, such as the neuromuscular signalling abnormalities seen in some patients with cervical cancer. The specific genes associated with the cell cycle can act as prognostic biomarkers and may also have an influence in mediating neuromuscular complications due to their impact on mitotic control and molecular signaling pathways throughout the body. This latter aspect is helpful for the prognosis of cancer, including cervical cancer, as well as for the multidisciplinary treatment of neuromuscular symptoms that some cervical cancer patients may have.

Key Words: cervical cancer; cell cycle genes; bioinformatics; differential gene expression; neuromuscular complications; prognosis.

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As an important component of gynaecological malignancies, cervical cancer is characterised by malignant proliferation and infiltrative metastasis of cervical epithelial cells. The latest global cancer statistics published by the International Agency for Research on Cancer (IARC) indicate, the disease presents significant prevalence characteristics in the spectrum of female malignancies: according to the data of the Global Status Report on Cervical Cancer Awareness 2023, in 2022, the global number of new cases of cervical cancer amounted to 661,021 (accounting for 3.3% of the new cancer cases in females), and the deaths of 342,000, and its age-standardized incidence and mortality rate ranked the fourth place for female malignant tumours.[1] Recent studies in China have shown that the incidence of cervical cancer has shown a tendency to spread to younger age groups in recent years, especially in the age range of 45 to 59 years, where the risk of cervical cancer significantly increases.[2] Standardized regular cervical cancer screening is crucial for the prevention and early detection of cervical cancer, allowing for more effective and timely treatment. From an etiological perspective, persistent infection with high-risk Human Papillomavirus (HPV) is identified as a major contributing factor,[3,4] HPV types 16 and 18 are responsible for around 70% of cervical cancer cases, although they only serve as a contributing factor for certain women. However, a single HPV infection by itself is insufficient to cause cervical cancer. Growing evidence indicates that dysregulated gene expression plays a pivotal role in the progression of this disease.[5] In recent years,

along with the continuous improvement of genomics and clinical databases, bioinformatics expression profiling data has become a new direction in tumour research. Gene chip is an emerging research tool developed in recent years, which has made a significant contribution to the study of diseases due to its high efficiency, ability to handle massive data, and wide applicability.[6] Based on the bioinformatics analysis method, this study systematically mined the gene expression comprehensive database for cervical cancer-related differentially expressed genes, and through in-depth analysis of the potential mechanisms of key genes, we aimed to provide theoretical basis for the early diagnosis of cervical cancer, and at the same time, lay the research foundation for the exploration of its molecular regulatory network and targeted therapeutic strategies.

Materials and Methods

Acquisition of data sets

This study obtained gene expression profile matrix files from four cervical cancer-related datasets (GSE63514, GSE6791, GSE52903, and GSE9750). The National Centre for Biotechnology Information (NCBI) offers access to the GEO database, which can be accessed via the link https://www.ncbi.nlm.nih.gov/geo/. This database contains several datasets relevant to cervical cancer research. The GSE63514 dataset consists of 28 cervical cancer tissues and 24 normal tissues. The GSE6791 dataset includes 20 cervical cancer samples alongside 8 normal control samples. Similarly, the GSE52903 dataset features 55 cases of cervical cancer and 17 healthy controls. Lastly, the GSE9750 dataset incorporates data from 33 cervical cancer patients and 24 normal tissue samples.

Data processing and identification of differentially expressed genes (DEGs)

In this study, four cervical cancer microarray datasets were analysed and processed using the R Studio software platform. The original gene expression profile matrix files were first converted into gene symbol matrices conforming to the international nomenclature specification using the R programming language. In the data preprocessing stage, probe data without corresponding gene names were excluded, and mean value processing was applied to the case of multiple probes mapping the same gene. The data normalization process was then completed using the Limma R software package, in which the expression values of the GSE9750 dataset were subjected to Log2 transformation. Based on the phenotypic information of the samples provided by the GEO database, the samples were divided into two comparison groups, the tumour tissue group and the normal tissue group, using the adjusted P-value <0.05 and the multiplicity of expression differences |Log 2 FC|>1 as the threshold criteria. After differential expression gene screening by the Limma R software package, the DEGs results from the four databases were finally integrated and cross-analyzed with the help of the Venn online analysis tool.

KEGG pathway and GO enrichment analysis

Metascape

(Https://metascape.or). The differentially expressed genes were input into the DAVID network platform for GO function enrichment analysis and KEGG pathway analysis, with P<0.05 as the screening result. The main results of enrichment were input into Microbiology (http://www.bioinformatics.com.cn/) online to make graphs.

Construction of protein interaction network and screening of key genes

Using the STRING database, we performed functional annotation and analysis (https://string-db.org) on the integrated differentially expressed genes. We selected proteins with a comprehensive score greater than 0.7 for Protein-Protein Interaction (PPI) analysis. The PPI relationships were visualized using Cytoscape3.9.1 software to construct a PPI network. Using the MCODE plugin, we identified closely associated gene modules. The genes within these modules were ranked using the Degree algorithm, and the top ten genes were selected as key genes.

Validation of key gene expression and survival analysis

This study employed the GEPIA online analysis platform (http://gepia.cancer-pku.cn/) to confirm the roles of pivotal genes identified during screening. Through a detailed assessment of their expression profiles in cervical cancer tissues, Kaplan-Meier survival analysis was conducted to create survival curves, aiming to explore the possible association between gene expression levels and clinical outcomes in cervical cancer patients. The data utilized for this analysis were obtained from the TCGA and GTEx databases, with parameters set to a box plot size of 0.4 and a significance threshold of $|\log2FC| > 1$ and $P < 0.01$.

Results

Screening results of differentially expressed genes

The GSE63514 dataset includes 2,259 upregulated genes and 1,269 downregulated genes. The GSE6791 dataset includes 1,496 upregulated genes and 717 downregulated genes. The GSE52903 dataset includes 345 upregulated genes and 573 downregulated genes. The GSE9750 dataset includes 583 upregulated genes and 1,467 downregulated genes. A VENN diagram analyzing the differentially expressed genes across these datasets reveals 89 upregulated and 28 downregulated genes, amounting to a total of 117 differentially expressed genes. This information is detailed in Table 1 and illustrated in Figure 1.

Constructing the PPI network and identifying key genes

The PPI network was developed using Cytoscape 3.7.0 software, with the resulting visualization displayed in Figure 2. Next, protein interactions were identified for the gene nodes using the STRING database, and the results were visualized using Cytoscape3.9.1 software, resulting in a protein interaction network diagram (Figure 2). To-

pological analysis was performed using the MCODE plugin to identify the top 10 key genes: KIF2C, NUSAPI, CDK1, CCNA2, KIF23, CDC20, EXO1, CENPF, UBE2C, and TOP2A (see Figure 3).

Enrichment function analysis

Through GO and KEGG pathway analyses, the findings from the GO functional analysis indicated a notable enrichment of various biological processes: mitotic cell cycle process, chromosome organization, cell division, regulation of cell cycle process, regulation of chromosome segregation, DNA metabolic process, cell cycle phase transition, meiotic cell cycle, mitotic spindle assembly, positive regulation of chromosome segregation, etc.; significant enrichment of cellular compositions enrichment: Chromosomal regions, spindle apparatus, nuclear chromosomes, centrosomes, microtubule-associated complexes, and cell cycle protein-dependent kinase holoenzyme complexes are mentioned. Notable enrichment is observed in molecular functions such as ATP-dependent activity, microtubule binding, chromatin binding, and regulatory activity of cell cycle protein-dependent serine/threonine kinases, among others. KEGG pathway analysis showed cell cycle, DNA instability, luteinizing hormone-mediated oocyte maturation, motor proteins, platinum drug resistance, and ubiquitin-mediated protein hydrolysis as the major pathways in Figure 4.

Expression verification of key genes

In this study, 5 key genes (CDK1, CCNA2, CDC20, TOP2A and EXO1) were selected from Figure 3, and the function of these key genes in cervical cancer expression

Table 1. *Differential gene expression in different databases.*

Data base	Tumour tissue group	Normal tissue group	Up-regulated gene	Downregulated genes	DEGs
GSE63514	28	224	2259	1269	3528
GSE6791	20	8	1496	717	2213
GSE52903	55	17	345	573	918
GSE9750	33	24	583	1467	2050

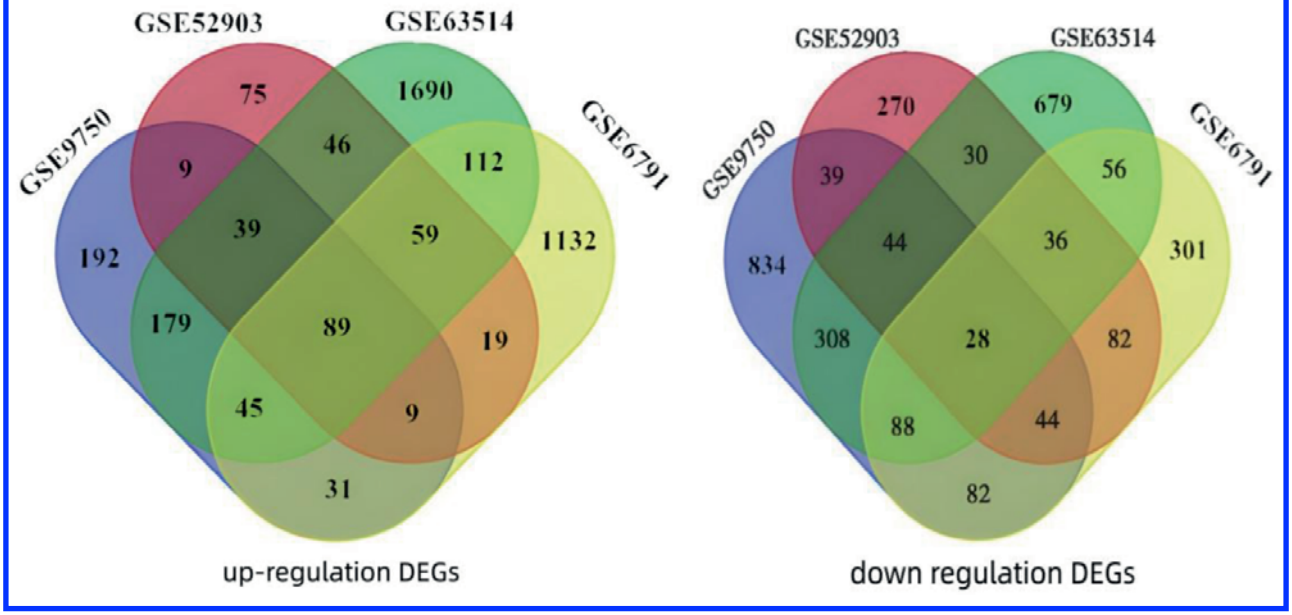

Figure 1. *VENN diagram of cervical cancer gene expression profiles associated with GSE63514, GSE6791, GSE52903 and GSE9750.*

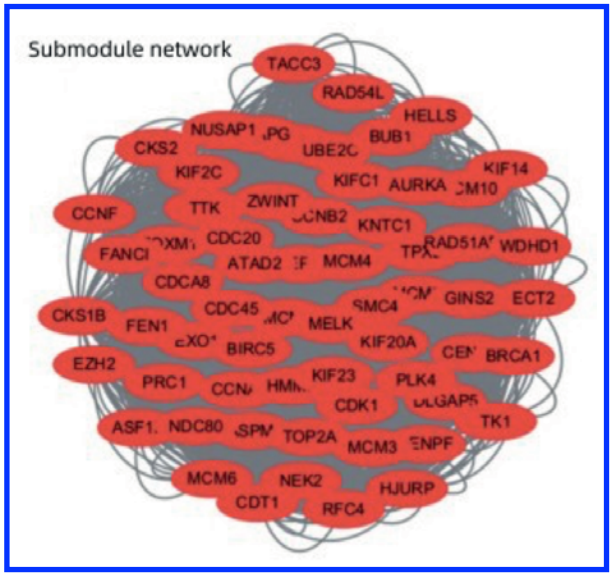

Figure 2. *PPI network of differential protein genes.*

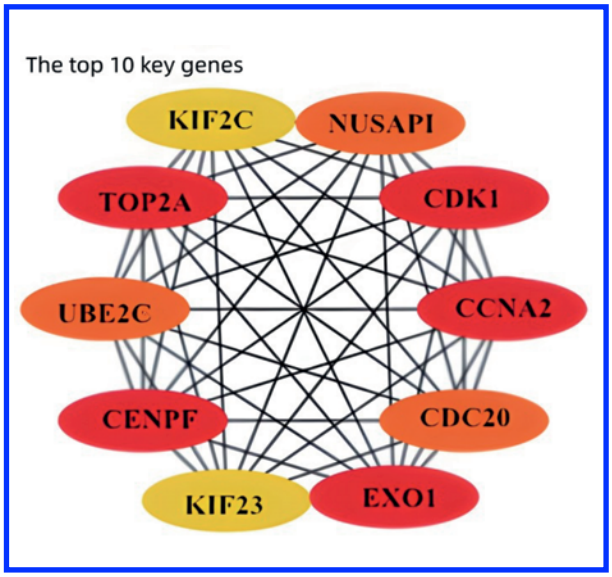

Figure 3. *Top 10 key genes.*

was verified by GEPIA. The study demonstrated that all five crucial genes showed significantly elevated expression levels in cervical cancer tissues (P<0.05), as illustrated in Figure 5.

Survival analysis of key genes

The GEPIA analysis of the five key genes showed a correlation between CCNA2 and cervical cancer staging (P<0.05) (see Figure 6). The BEST analysis of these key genes revealed that CCNA2 is associated with a shorter DFS in cervical cancer (P<0.05), while CDK1 is linked to a longer OS (P<0.05) (see Figures 7 and 8).

Discussion

Cervical cancer remains the most prevalent form of cancer affecting women, representing a serious risk to both their health and lives. The International Federation of Gynaecology and Obstetrics (FIGO) recommends radical hysterectomy paired with pelvic lymphadenectomy as the standard treatment for early-stage cervical cancer. While laparoscopic pelvic lymphadenectomy has been introduced in later stages, it still carries risks of recurrence and metastasis, and there are currently no effective treatment options for recurrent cases.[7,8] Therefore, identifying effective early diagnostic methods and specific biomarkers for cervical cancer is crucial for improving patient outcomes. With the rapid advancement of bioinformatics, researchers can now use high-throughput data analysis to effectively identify abnormal expression patterns of disease-related genes, providing more precise molecular evidence for clinical diagnosis and opening new avenues for discovering potential biomarkers related to prognosis.[9] This study uses the key gene spectrum from the GEO database to investigate the expression of key genes in cervical cancer and their correlation with prognosis.

This study identified 117 genes exhibiting significant expression differences through a systematic analysis of four independent datasets from the GEO database. Among these, 89 genes were found to be up-regulated, while 28 were down-regulated. Protein interaction network analysis based on the STRING database further screened the 10 core genes with the highest connectivity in the network. Using GO and KEGG pathway analysis, it was found that the results of GO functional analysis showed significant enrichment of involved molecular functions, mainly focused on ATP-dependent activity, microtubule binding, and chromatin binding. The study highlights the regulatory activity of cell cycle protein-dependent serine/threonine kinases and other related functions. KEGG pathway analysis identified several significant pathways, including the cell cycle, DNA replication, luteinizing hormone-driven oocyte maturation, motor protein activity, platinum drug resistance, and ubiquitin-mediated protein degradation as pivotal processes. Key genes—CDK1, CCNA2, CDC20, TOP2A, and EXO1—were chosen for validation. Findings revealed that these genes were significantly overexpressed in cervical cancer tissues (P < 0.05).

CCNA2 is a crucial cell cycle regulator that activates cyclin-dependent kinase 2, controlling the transition of the cell cycle from G1/S to G2/M, playing a vital role in cell proliferation.[10] Therefore, CCNA2 is a key factor in regulating cell proliferation and division, closely linked to the development of various solid tumours. Additionally, CCNA2 is involved in multiple tumour Epithelial-Mesenchymal Transitions (EMTs), which are closely associated with tumour invasion and metastasis, and are closely related to the prognosis of several types of cancer, including colon, pancreatic, gastric, breast, renal, lung, and bladder cancers.[11-14]

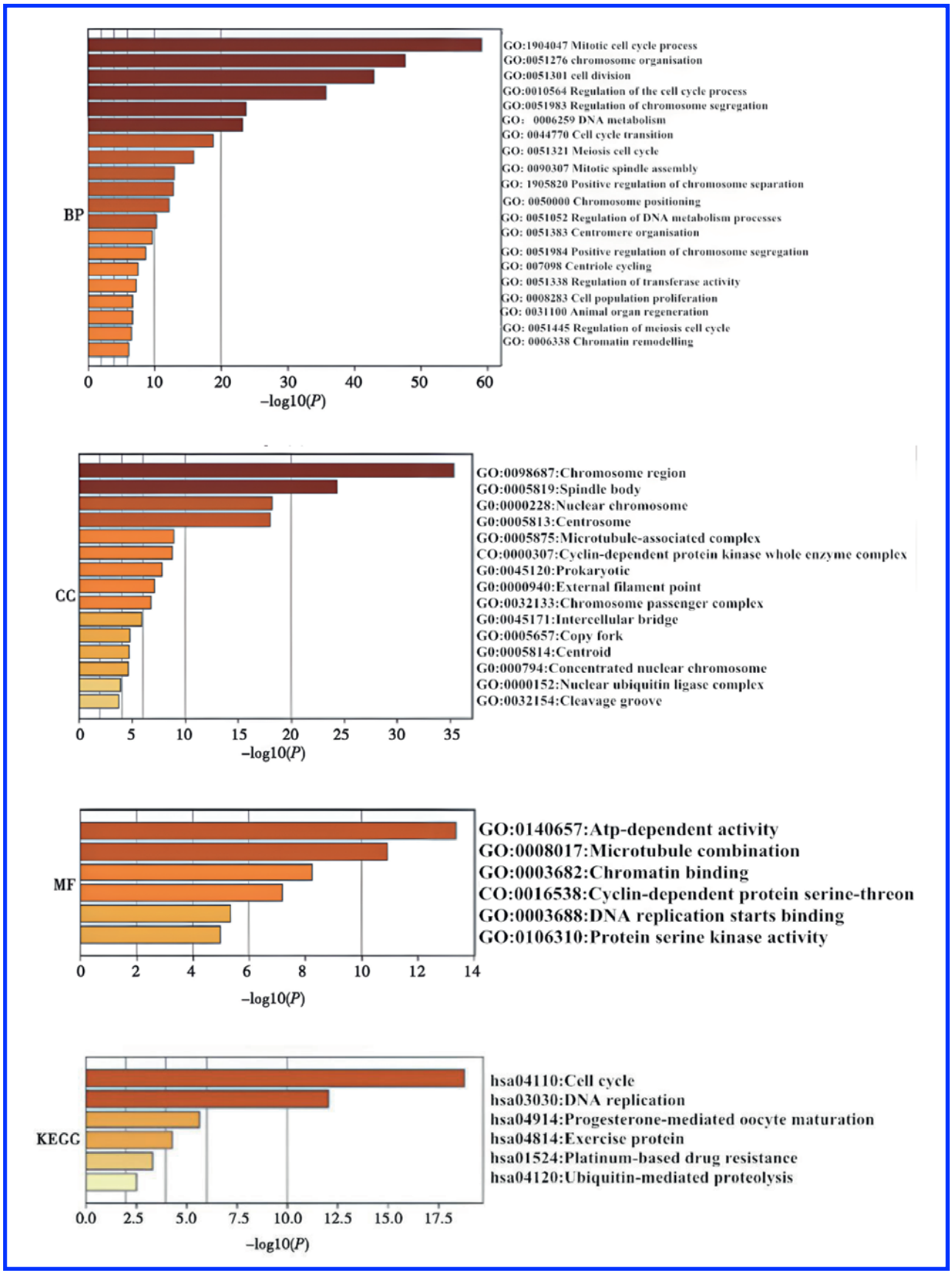

Figure 4. *GO and KEGG pathway analysis of differentially expressed genes.*

This study suggests that CCNA2 plays a significant role in promoting cervical cancer progression and has the potential to become a new tumour marker. CDK1, also known as cyclin-dependent kinase 1, is a crucial regulatory factor that plays a critical role in processes such as cell mitosis and DNA replication, and is also widely involved in regulating various cell cycles, with high expression in most cancers. Research indicates that CDK1 can promote the phosphorylation of telomerase, thereby facilitating tumour development.[15] This study highlights the crucial role of CDK1 in the development and progression of cervical cancer. CDC20, also known as cyclin 20, is a protein kinase that regulates the cell cycle, affecting cell division and chromosome separation. Its expression is strongly regulated in various malignant tumours, such as liver cancer, pancreatic cancer, and gastric cancer.[16-18] Inhibiting CDC20 expression can prevent the Epithelial-to-Mesenchymal Transition (EMT) of glioblastoma drug-resistant cell lines and affect their proliferation.[19] This study highlights the significant role of CDC20 in driving the development and progression of cervical cancer, particularly due to its elevated expression levels. TOP2A, a crucial transcription factor, is involved in DNA synthesis, transcription, and chromosome segregation. It

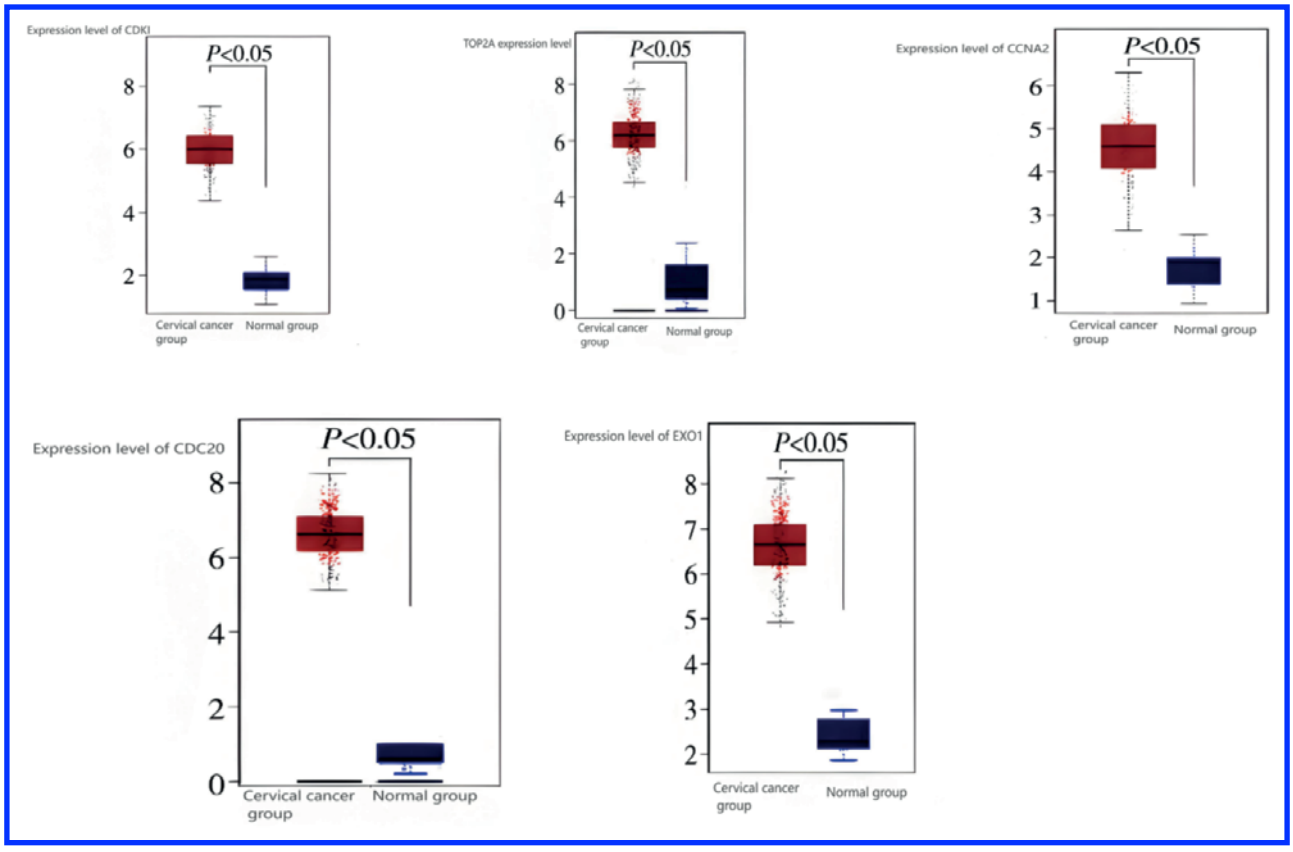

Figure 5. *Verification of the expression level of key genes.*

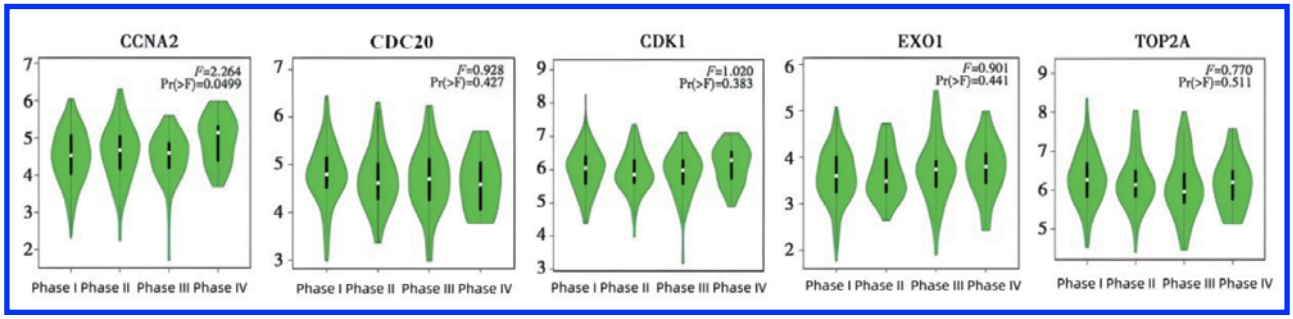

Figure 6. *Correlation between key genes and cervical cancer staging.*

is a specific tumour marker, showing significantly high expression during the S phase, G2 phase, and M phase, and is closely associated with poor tumour prognosis.[20] EXO1, a class of 5 'to 3' end nucleases, is involved in DNA damage repair. Literature reports that EXO1 is highly expressed in various tumours, including liver cancer, breast cancer, and astrocytoma, and is associated with poor patient outcomes.[21] The survival analysis in this study shows that CCNA2 and CDC20 are associated with shorter DFS in cervical cancer ($P<0.05$), and CCNA2 is associated with shorter DFS in cervical cancer ($P<0.05$). Additionally, CDK1 is associated with shorter OS in cervical cancer ($P<0.05$), suggesting that CDK1, CCNA2, CDC20, TOP2A, and EXO1 are related to the prognosis of cervical cancer, which aligns with the findings of other researchers. Biological markers have demonstrated significant clinical application value in the field of cervical cancer diagnosis and treatment, and are expected to provide new references for the formulation of clinical diagnosis and treatment.

Although our primary focus was on cervical cancer, some of the key genes we identified, like CDK1 and CCNA2, have also been linked to neuromuscular functions. Alterations in cell cycle regulatory genes may impair muscle repair processes, impact mitochondrial function, and disrupt the integrity of neuromuscular junctions. For this reason, these genes may play a role in the neuromuscular complications seen in patients with advanced stages of cancer or in those who have undergone cancer treatments. More mechanistic studies are needed to investigate this relationship.

Exploring the link between cell cycle gene dysregulation and neuromuscular complications in cervical cancer

Although cervical cancer is mainly characterized as a condition arising from uncontested growth of cells, there is an emerging perspective that the genes controlling the cell cycle and associated with cancer may, indeed, have an impact on systemic functions such as neuromuscular physiology. In this research, some hub genes such as CDK1, CCNA2, and CDC20 were found to be markedly overexpressed in cervical cancer tissues. These genes are important for mitosis, DNA replication, and chromosome segregation; however, their impact goes beyond the realm of oncology and may also affect neuromuscular homeostasis, especially in the setting of cancer-induced systemic derangement or due to toxicity from treatment.

CDK1, a cyclin-dependent kinase that governs cell cycle transitions, has been shown to regulate mitochondrial fission through phosphorylation of dynamin-related protein 1 (Drp1), affecting energy metabolism and Reactive Oxygen Species (ROS) balance in skeletal muscle tissue.[22] Dysregulation of CDK1 may impair mitochondrial quality control, a process vital for maintaining muscle contractility and neuromuscular transmission. Consequently, aberrant CDK1 expression may contribute to muscle atrophy, weakness, and cancer-associated fatigue, which are common in advanced cancer patients.

Similarly, CCNA2 (Cyclin A2) has also seen action beyond its canonical role in the G1/S and G2/M phase transitions by also participating in the advancement of neural progenitor cells as well as their differentiation.[23] Change in the normal functioning and alteration of repair mech-

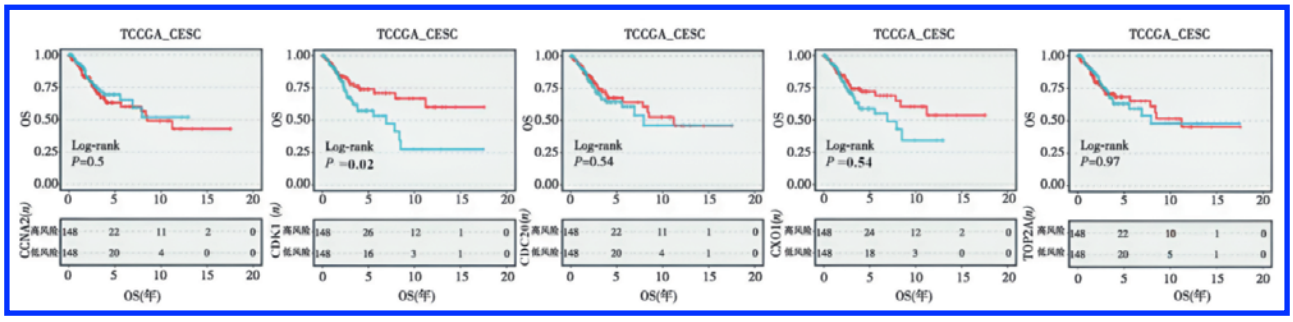

Figure 7. Correlation between key genes and cervical cancer OS.

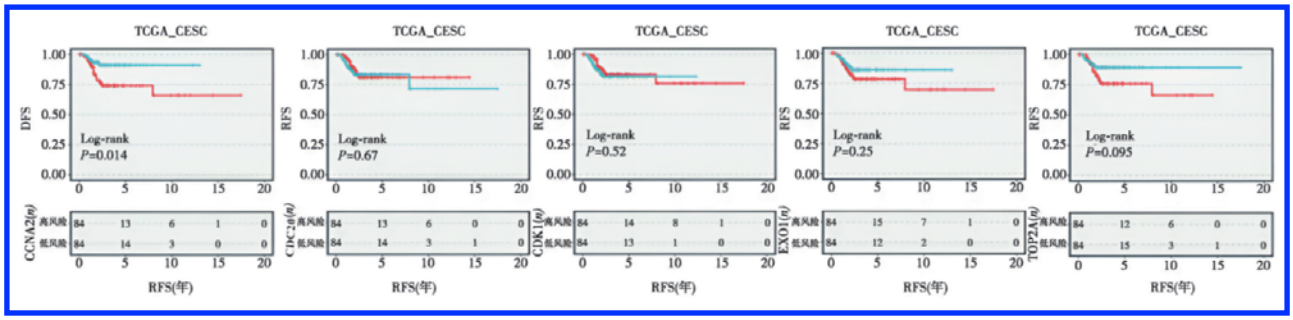

Figure 8. Correlation between key genes and cervical cancer DFS.

anisms during neurogenesis have been noted with the overexpression of CCNA2 in the central and peripheral nervous systems. The expression profile of CCNA2, along with the common treatment of cervical cancer patients with genotoxic radiation or oestrus therapeutics, may promote peripheral neuropathy following chemotherapy CIPN and harm to the neuromuscular junction by diminished regenerative potential of the neural tissue.

CDC20, another cell cycle regulator critical for Anaphase-Promoting Complex (APC) activation, has been associated with neuronal apoptosis under oxidative stress and metabolic strain.[24] Its dysregulation may further disrupt cellular homeostasis in neurons and muscle satellite cells, contributing to delayed repair and degeneration in neuromuscular tissues.

In addition to the intrinsic gene effects, therapies targeting these pathways introduce further complexity. CDK inhibitors, used in various cancers, including cervical cancer trials, have been associated with neuromuscular adverse effects such as myopathy, paresthesia, and motor dysfunction.[25] These observations underscore the possibility that both tumour-driven molecular alterations and the iatrogenic effects of targeted therapies may converge to impact neuromuscular systems in cervical cancer patients.

It is essential to know how oncogenic gene signatures work together with diffuse neuromuscular complications. With the advancement of precision oncology, the assessment of systemic gene expression profiles may aid not only in forecasting tumour advancement but also in predicting treatment-associated comorbidities. This study's discovery of pivotal cell cycle genes that have been upregulated in cervical cancer poses the possibility of studying their more profound physiological ramifications. Discoveries from this investigation on the expression of CDK1, CCNA2, and CDC20 and their muscle and nerve tissue responsive alterations require *in vitro* and *in vivo* model testing to confirm these conjectures will be critical.

Ultimately, integrating bioinformatics insights with clinical symptomatology may help clinicians anticipate, monitor, and mitigate neuromuscular side effects, leading to improved quality of life in cervical cancer patients undergoing systemic therapies.

Conclusions

In summary, the expression of CDK1, CCNA2, CDC20, TOP2A, and EXO1 genes in cervical cancer tissues has shown significant changes, which are closely linked to tumour prognosis. These genes have the potential to act as biomarkers for the early detection and prognosis of cervical cancer. However, this study has certain limitations; the existing data is limited to small samples and lacks general applicability. Therefore, future studies should expand the sample size, analyze their relationship with clinical indicators of cervical cancer, clarify their diagnostic value, and enhance accuracy and practicality.

Future research should prioritize validating these biomarkers in larger clinical populations and investigating their underlying mechanisms of cervical cancer and neuromuscular complications.

List of abbreviations

DEGs, Differentially Expressed Genes
GO, Gene Ontology
KEGG, Kyoto Encyclopedia of Genes and Genomes
PPI, Protein-Protein Interaction
GEO, Gene Expression Omnibus
NCBI, National Center for Biotechnology Information
FC, Fold Change
IARC, International Agency for Research on Cancer
HPV, Human Papillomavirus
1FIGO, International Federation of Gynaecology and Obstetrics
1TCGA, The Cancer Genome Atlas
1GTEx , Genotype-Tissue Expression
1GEPIA, Gene Expression Profiling Interactive Analysis
1DFS, Disease-Free Survival
1OS, Overall Survival
1EMT, Epithelial-Mesenchymal Transition
APC, Anaphase-Promoting Complex
ROS, Reactive Oxygen Species
CIPN, Chemotherapy-Induced Peripheral Neuropathy
CDK1, Cyclin-Dependent Kinase 1
CCNA2, Cyclin A2
CDC20, Cell Division Cycle 20

Conflict of interest

The authors declare no potential conflict of interest, and all authors confirm accuracy.

Ethics approval

The Ethics Committee of Affiliated Hospital of Chifeng University approved this study (fsyy2024062). The study is conformed with the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights.

Informed consent

All patients participating in this study signed a written informed consent form for participating in this study. Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Corresponding author

Huijuan Qi, Department of Gynecology, Affiliated Hospital of Chifeng University, Chifeng City 024000, China.
ORCID ID: 0000-0002-6859-9959
E-mail: cfxyqihuijuan1968@163.com

Co-authors

Xiaojing Liu
ORCID ID: 0009-0004-5393-4605
E-mail: 15047660000@163.com

Jialiang Sun
ORCID ID: 0009-0009-8847-2240
E-mail: 362268090@qq.com

Lina Dong
ORCID ID: 0009-0008-4785-1642
E-mail: qhh4303@gmail.com

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