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ORIGINAL RESEARCH

Bioinformatic Analysis for the Prognostic Implication of Genes Encoding Epithelial Sodium Channel in Cervical Cancer

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Background: Cervical cancer is one of the leading causes of death in women. Among the sodium ion channels associated with cancer development, voltage gated sodium channel plays an important role in pathophysiology of cervical cancer; however, the clinicopathological implication of epithelial sodium channel (ENaC) has not been explored.

Purpose: This study focused on identifying dysregulation of ENaC encoding genes, including *SCNN1A, SCNN1B*, and *SCNN1G*, and their relationship with clinicopathologic features in cervical cancer patients.

Materials and Methods: RNA sequencing data of ENaC-encoding genes, clinicopathologic data, and survival data of cervical cancer patients were obtained from The Cancer Genome Atlas cohort. Microarray data of ENaC-encoding genes were obtained from Gene Expression Omnibus datasets: GSE6791 and GSE63514.

Results: The expression levels of *SCNN1A, SCNN1B*, and *SCNN1G* were positively correlated with each other. *SCNN1A, SCNN1B*, and *SCNN1G* are significantly overexpressed in normal tissues than in tumor tissues. Survival analysis showed that simultaneous overexpression of all three genes associated with better overall survival (OS). Each overexpression of *SCNN1B* and *SCNN1G* was significantly associated with better OS. Moreover, each expression level of *SCNN1A, SCNN1B*, and *SCNN1G* was negatively correlated with histologic grade of tumor.

Conclusion: ENaC-encoding genes might be potential biological markers to better predict survival outcomes in cervical cancer patients.

Keywords: sodium ion channel, cervical cancer, survival outcome, ENaC-encoding genes

Introduction

Cervical cancer arises from cells in the cervix and is one of the leading causes of death in women worldwide.[1] High-risk human papilloma virus (HPV) infection, early first sexual intercourse, and multiple sexual partners are the well-known risk factors for cervical cancer.[2,3] The mechanism of carcinogenesis associated with HPV in cervical cancer was discovered recently.[4] This enabled the development of vaccination strategies to reduce cervical cancer incidence. Additionally, wide applications of screening tests, such as Pap test and HPV detection test, have facilitated early detection of cervical cancer. However, the incidence of cervical cancer from country to country and is still one of the most common causes of cancer-related deaths in women.[5–8] Although the prognostic factors for cervical cancer are well known, it is difficult to predict the prognosis due to heterogenic treatment outcome in cervical cancer patients.[9] Therefore, it is necessary to understand the biological features of cervical cancer and identify factors that can predict cervical cancer prognosis.

In humans, two major classes of sodium channels have been reported: voltage gated sodium channel (VGSC) and non-voltage gated sodium channel or epithelial sodium channel (ENaC).[10] VGSC consists of a single pore-forming large

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α-subunit, and one or more β-subunits. VGSC regulates action potential in cells.[11] In contrast, ENaC is a member of degenerin/ENaC superfamily. It consists of three subunits α, β, and γ, which are encoded by *SCNN1A, SCNN1B*, and *SCNN1G*, respectively. ENaC is expressed mainly in epithelial cells and transports sodium ions across the apical membranes, which play an important role in the maintenance of sodium and water homeostasis.[12,13] Some studies have shown that VGSC and its subunits are associated with cervical cancer development, suggesting them as new therapeutic targets.[14–18] However, the relationship between ENaC and cervical cancer remains unknown.[19] In this study, we investigated the expression of ENaC-encoding genes and their clinicopathological implications in cervical cancer using Gene Expression Omnibus (GEO) dataset and The Cancer Genome Atlas (TCGA) cohorts.

Materials and Methods

Microarray Data Source and Data Mining

The gene expression microarray datasets of cervical cancer patients used in the present study, GSE63514[20] and GSE6791,[21] were downloaded from the publicly available GEO database (National Institutes of Health, Bethesda, MD, USA; http://www.ncbi.nlm.nih.gov/geo). We obtained 18 datasets using "cervical cancer", "normal cervix tissue", "Homo sapiens" and "GPL570 platform" as keywords. Among these, datasets including both normal cervix tissue and cancer tissue without treatment with chemotherapy or radiotherapy were selected, which resulted in two datasets. The basic information related to the two datasets is listed in Table 1. Both datasets used the GPL570 platform (Affymetrix, GeneChip Human Genome U133 Plus 2.0 Array). The Affymetrix ID is valid: 203453_at (*SCNN1A*), 205464_at (*SCNN1B*), and 207295_at (*SCNN1G*). GSE63514 contains gene expression data of 24 normal cervix tissues, 14 cervical intraepithelial neoplasia (CIN) lesions, 22 CIN2 lesions, 40 CIN3 lesions, and 28 cervical cancer tissues.[20] GSE6791 comprises gene expression information of eight normal cervix tissue samples, 20 cervix tissue samples of cervical cancer patients, 42 head and neck cancer tissue samples, and 14 normal head and neck tissue samples.[21] Moreover, the expression of *SCCN1A, SCCN1B*, and *SCNN1G*, was analyzed in 32 normal cervix tissue samples and 48 cervical cancers using tissue samples from the two datasets.

Data Normalization and Background Correction

Affy package (version 1.68.0; Bioconductor.org/packages/release/bioc/html/affy.html) in R language (version 3.4.1; http://cran.r-project.org/) was utilized for processing raw data downloaded from the GEO database. All expression profiling data were merged, and background correction followed by normalization was conducted using Robust Multi-array Average (RMA) algorithm and quantile normalization.[22] The Student's *t*-test was used to analyze the differences in gene expression levels between normal and tumor tissues. Then, the results, log2 fold change (logFC) and box plot of gene expression, were plotted using R language. Results with $P < 0.05$ were considered to be statistically significant.

Gene Ontology Analysis of SCNN1A, SCNN1B and SCNN1G

The Database for Annotation, Visualization, and Integrated Discovery (DAVID) online software v6.8 (http://david.ncifcrf.gov/) was utilized to analyze the biological implications of the expressions of ENaC encoding genes. The Gene Ontology (GO) terms were subcategorized into biological process (BP), cellular component (CC), and molecular function (MF). Results with $P < 0.05$ were considered to be statistically significant.

Table 1 Basic Information of Microarray Data from NCBI GEO Database

Platform	GEO Dataset	Samples	Reference
GPL570	GSE63514 GSE6791	24 Normal, 28 Cancer 8 Normal, 20 Cancer	Den Boom, Johan A. et al.[20] Pyeon, Dohun et al.[21]

Abbreviations: NCBI, the national center for biotechnology information; GEO, gene expression omnibus.

Data Source for Analyzing Association with Clinicopathology

The RNA-sequencing data for gene expression (dataset ID: TCGA.CESC.sampleMap/HiSeqV2) and clinicopathological parameters (dataset ID: TCGA.CESC.sampleMap/CESC_clinicalMatrix) of cervical cancer patients were downloaded from the USCS Xena Browser (http://xenabrowser.net/). The evaluated RNA-seq dataset includes 308 samples. Patients for whom survival information or gene expression data information were not available were excluded. The gene expression levels were quantified as log2(x+1) transformed RNA-Seq by Expectation Maximization (RSEM) normalized counts. To analyze clinicopathological features, the patients were grouped into higher and lower expression groups by dividing them at a cutoff value of the median expression of each gene. The clinicopathological features included age at diagnosis, clinical stage at diagnosis, histological grades, tumor status, presence of lymphatic invasion, response to primary therapy, and presence of new tumor after primary therapy. This study met the publication guidelines provided by TCGA (http://www.cancer.gov/about-nci/organization/ccg/research/structrual-genomics/tcga/using-tcga/citing-tcga).

Survival Analysis of SCNN1A, SCNN1B, and SCNN1G

The survival data of cervical cancer patients (dataset ID: survival/CESC_survival) was downloaded from the USCS Xena Browser. For the survival analysis, the patients were grouped into higher and lower expression groups by dividing them at a cutoff value of the median expression of each gene. Patients for which survival data were not available were excluded. The data were subjected to Kaplan–Meier survival analysis and Cox regression using SPSS software (version 27.0; IBM SPSS, Armonk, NY, USA). Results with $P < 0.05$ were considered to be statistically significant.

Statistical Analysis

SPSS software (version 27.0; IBM SPSS, Armonk, NY, USA) was used to analyze the data. The association between gene expression and clinical information was analyzed using Pearson's Chi-square test for categorical variables. The correlation between expression of each gene and histologic grade was determined using Pearson's correlation coefficient analysis. Results with $P < 0.05$ were considered to be statistically significant. Comparison of gene expression between normal and cancer tissue was analyzed using R. Levene's test was performed to analyze the equality of variances. $P < 0.05$ indicated a non-parametric distribution of variances. The Student's *t*-test was performed to analyze differences in gene expression between normal and cancer tissues. $P < 0.05$ was considered statistically significant.

Results

SCNN1A, SCNN1B, and SCNN1G Expression Levels are Positively Correlated with Each Other

Pearson's correlation coefficient analysis was performed using gene expression data of cervical cancer patients in TCGA cohort. The result showed the expression levels of these genes are positively related to each other. Additionally, there was a stronger relationship between *SCNN1B* and *SCNN1G* expression ($r = 0.816$, $P < 0.001$) than between *SCNN1A* and *SCNN1B* expression ($r = 0.343$, $P < 0.001$) or *SCNN1G* expression ($r = 0.226$, $P < 0.001$) (Figure 1). The online tool DAVID was used to analyze GO terms of *SCNN1A, SCNN1B*, and *SCNN1G*. The expression of these genes is mainly involved in water homeostasis, sodium ion transport, and homeostasis in multicellular organisms. Interestingly, expressions of *SCNN1B* and *SCNN1G*, and not *SCNN1A*, are involved in excretion (GO: 0007588), a process through which metabolic wastes such as carbon dioxides and nitrogenous compounds are eliminated from the cells, and mainly enriched in the outer leaflet of the plasma membrane (Table 2).

SCNN1A, SCNN1B, and SCNN1G are Overexpressed in Normal Tissue Than in Cancer Tissue

The expression of *SCNN1A, SCNN1B*, and *SCNN1G* between normal and tumor tissues was analyzed using data downloaded from the GEO dataset GSE 63514 and GSE6791. Based on the GSE 63514 and GSE6791 datasets, gene expression data of 32 normal cervix tissue samples and 48 cervix tissue samples from cervical cancer patients were analyzed. The result showed that the expression levels of *SCNN1A* ($P = 2.73E-03$, $logFC = -0.8520$), *SCNN1B* ($P =$

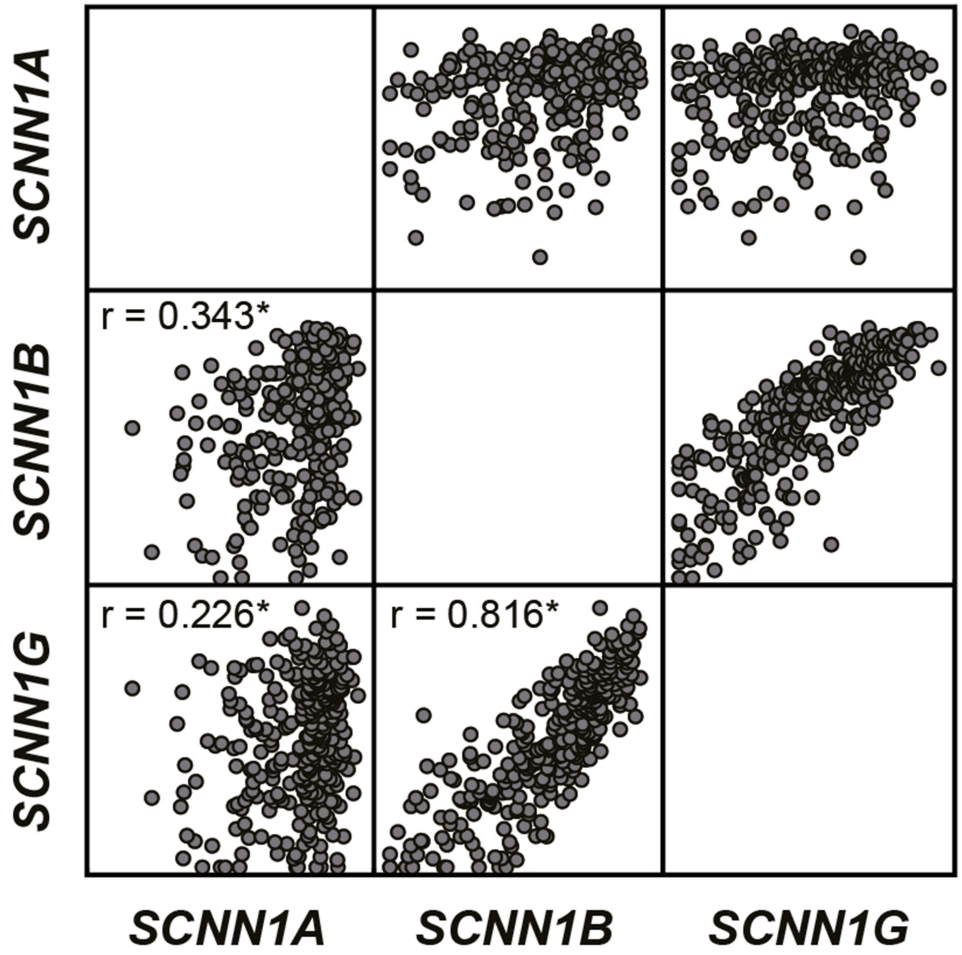

Figure 1 Inter-individual correlation among ENaC encoding genes in cervical cancer samples. Association among mRNA expression levels of *SCNN1A, SCNN1B*, and *SCNN1G* based on The Cancer Genome Atlas data. *P < 0.001.
Abbreviation: r, Pearson's correlation coefficient.

4.89E-16, logFC = −2.325162), and *SCNN1G* (P = 1.45E-05, logFC = −0.434747) were higher in normal tissues than in tumor tissues (Figure 2).

Survival Analysis of the Dysregulated SCNN1A, SCNN1B, and SCNN1G in Cervical Cancer Patients

The survival data of cervical cancer patients in TCGA cohort was subjected to Kaplan–Meier survival analysis using SPSS. After excluding patients for which gene expression data or survival data were not available, 307 patients were included. First, we compared survival data of 83 cervical cancer patients who showed overexpression of all three genes against 84 patients who showed lower expression of all three genes. The result showed that overexpression of *SCNN1A, SCNN1B*, and *SCNN1G* was associated with better overall survival (OS) in cervical cancer patients (P = 0.04, HR = 0.496, 95% CI: 0.251–0.983). Next, we examined the relationship between the expression of each gene and the survival of cervical cancer patients. The KM plot and Log rank test demonstrated that higher expression of *SCNN1B* (P = 0.007, HR = 0.524, 95% CI: 0.326–0.841) and *SCNN1G* (P = 0.02, HR = 0.575, 95% CI: 0.359–0.921) was associated with better OS, while *SCNN1A* expression alone did not affect the OS of cervical cancer patients (Figure 3).

Table 2 GO Terms of *SCNN1A, SCNN1B*, and *SCNN1G*

Category	Term	Gene Names	P value
GO_BP	GO:0050891 Multicellular organismal water homeostasis	*SCNN1A, SCNN1B, SCNN1G*	2.0E-7
	GO:0055078 Sodium ion homeostasis	*SCNN1A, SCNN1B, SCNN1G*	3.9E-7
	GO:0050909 Sensory perception of taste	*SCNN1A, SCNN1B, SCNN1G*	2.9E-6
	GO:0050896 Response to stimulus	*SCNN1A, SCNN1B, SCNN1G*	1.3E-5
	GO:0035725 Sodium ion transmembrane transport	*SCNN1A, SCNN1B, SCNN1G*	1.9E-5
	GO:0034220 Ion transmembrane transport	*SCNN1A, SCNN1B, SCNN1G*	1.6E-4
	GO:0007588 Excretion	*SCNN1B, SCNN1G*	4.4E-3
	GO:0006814 Sodium ion transport	*SCNN1B, SCNN1G*	9.6E-3
GO_CC	Sodium channel complex	*SCNN1A, SCNN1B, SCNN1G*	6.0E-8
	Apical plasma membrane	*SCNN1A, SCNN1B, SCNN1G*	2.5E-4
	Integral component of plasma membrane	*SCNN1A, SCNN1B, SCNN1G*	6.0E-3
	External side of plasma membrane	*SCNN1B, SCNN1G*	2.3E-2
	Extracellular exosome	*SCNN1A, SCNN1B, SCNN1G*	2.4E-2
GO_MF	Ligand-gated sodium channel activity	*SCNN1A, SCNN1B, SCNN1G*	2.0E-7
	Sodium channel activity	*SCNN1A, SCNN1B, SCNN1G*	7.4E-7
	WW domain binding	*SCNN1A, SCNN1B, SCNN1G*	3.3E-6

Abbreviations: GO, Gene Ontology; BP, biological process; CC, cellular component; MF, molecular function.

SCNN1A, SCNN1B, and SCNN1G Overexpression is Associated with Lower Histologic Grade of Cervical Cancer

The association between the clinicopathologic features of cervical cancer patients and the expressions of *SCNN1A, SCNN1B*, and *SCNN1G* was analyzed. The data included information related to histologic grades and gene expression levels in 276 patients with cervical cancer. The result showed that an increased expression of all three genes was associated with lower histologic grade of tumor, although it did not affect other clinicopathologic features (Table 3). Moreover, analysis of correlation between expression level of *SCNN1A, SCNN1B*, and *SCNN1G* and histologic grade

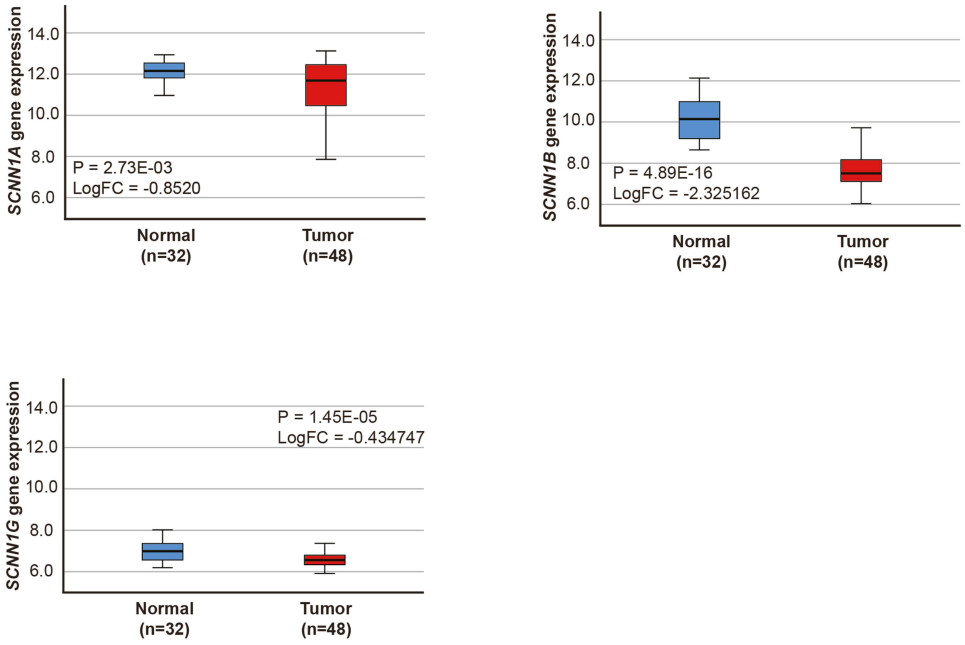

Figure 2 Box plots presenting relative expression levels of *SCNN1A, SCNN1B*, and *SCNN1G* between normal and tumor tissues.
Abbreviation: LogFC, Log2 fold change.

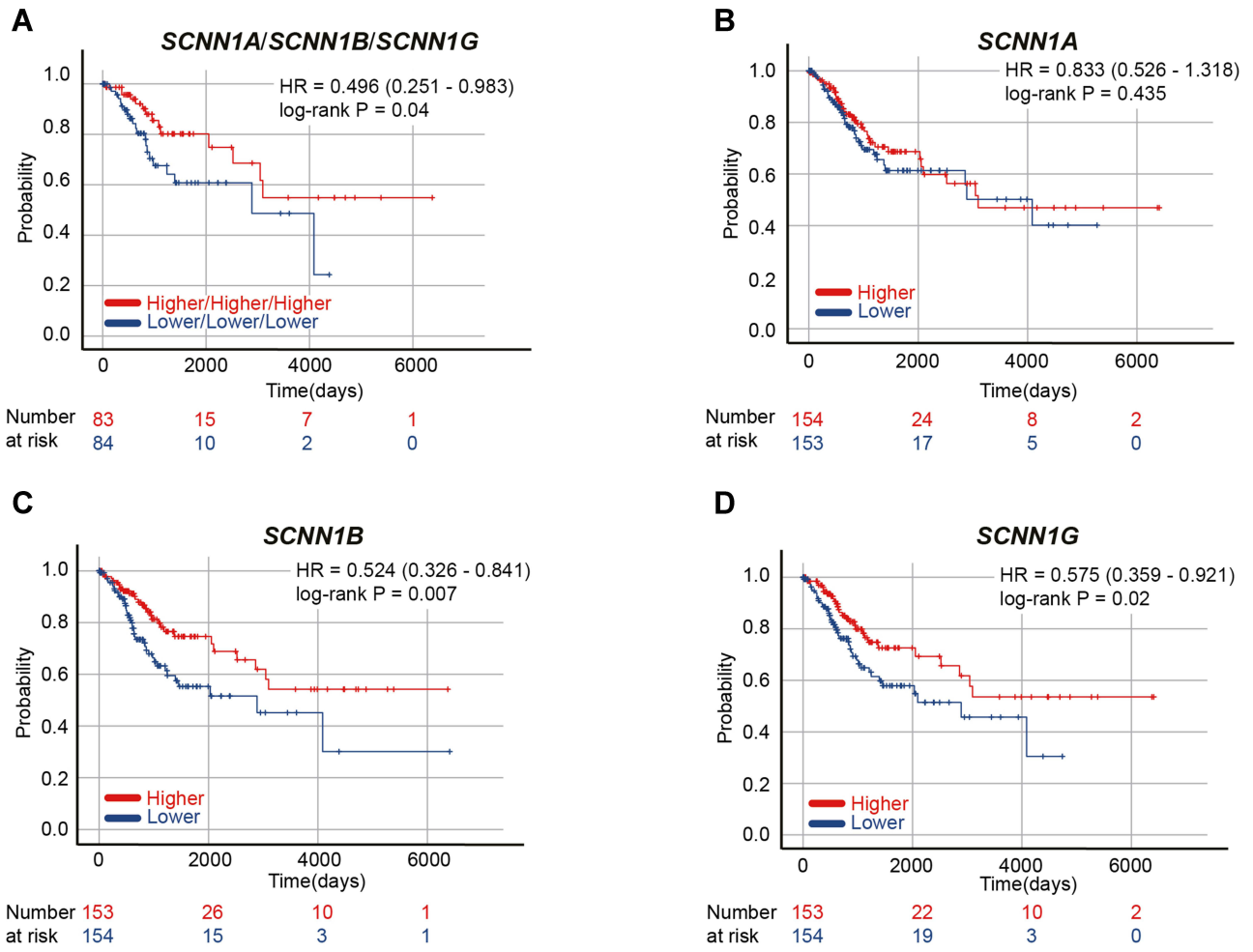

Figure 3 Survival analysis of the dysregulated *SCNN1A, SCNN1B*, and *SCNN1G* in cervical cancer patients. Kaplan–Meier analysis of patients with cervical cancer according to the relative mRNA expression levels of *SCNN1A, SCNN1B*, and *SCNN1G* (**A**), *SCNN1A* (**B**), *SCNN1B* (**C**), and *SCNN1G* (**D**).
Abbreviation: HR: hazard ratio with 95% confidential interval in brackets.

showed that histologic grade and mean expression levels of *SCNN1A, SCNN1B*, and *SCNN1G* were negatively correlated (Figure 4 and Table 4).

Discussion

Cervical cancer is the fourth most common cancer in women, and approximately 570,000 new cases and 311,000 deaths were reported in 2018 worldwide.[23] Although HPV vaccination, along with wide utilization of Pap screening test and HPV detection test, has led to a significant decrease in the incidence rate of cervical cancer, cervical cancer remains one of the most common cancers and one of the leading causes of death in women.[7,24] Despite the presence of various prognostic factors such as age at diagnosis, clinical stage, lymphatic spread, residual tumor status, and histologic grade of tumor,[25] there have been efforts to identify more reliable factors for predicting patient prognosis and unravel the molecular mechanisms related to cervical cancer pathogenesis.

ENaC is a non-voltage gated sodium channel, and plays a key role in maintaining sodium and water homeostasis.[12] Recent studies have focused beyond the physiologic functions of ENaC and aimed to investigate its role in cancer cell biology.[19,26] However, the inter-relationship between ENaC encoding genes and the prognostic significance and clinical implications of ENaC gene expression in cervical cancer remains unclear. In the present study, we focused on microarray and RNA-sequencing data of ENaC encoding genes, *SCNN1A, SCNN1B*, and *SCNN1G*, and their clinicopathological correlation in cervical cancer patients. The results showed that the expression levels of *SCNN1A, SCNN1B*, and *SCNN1G*

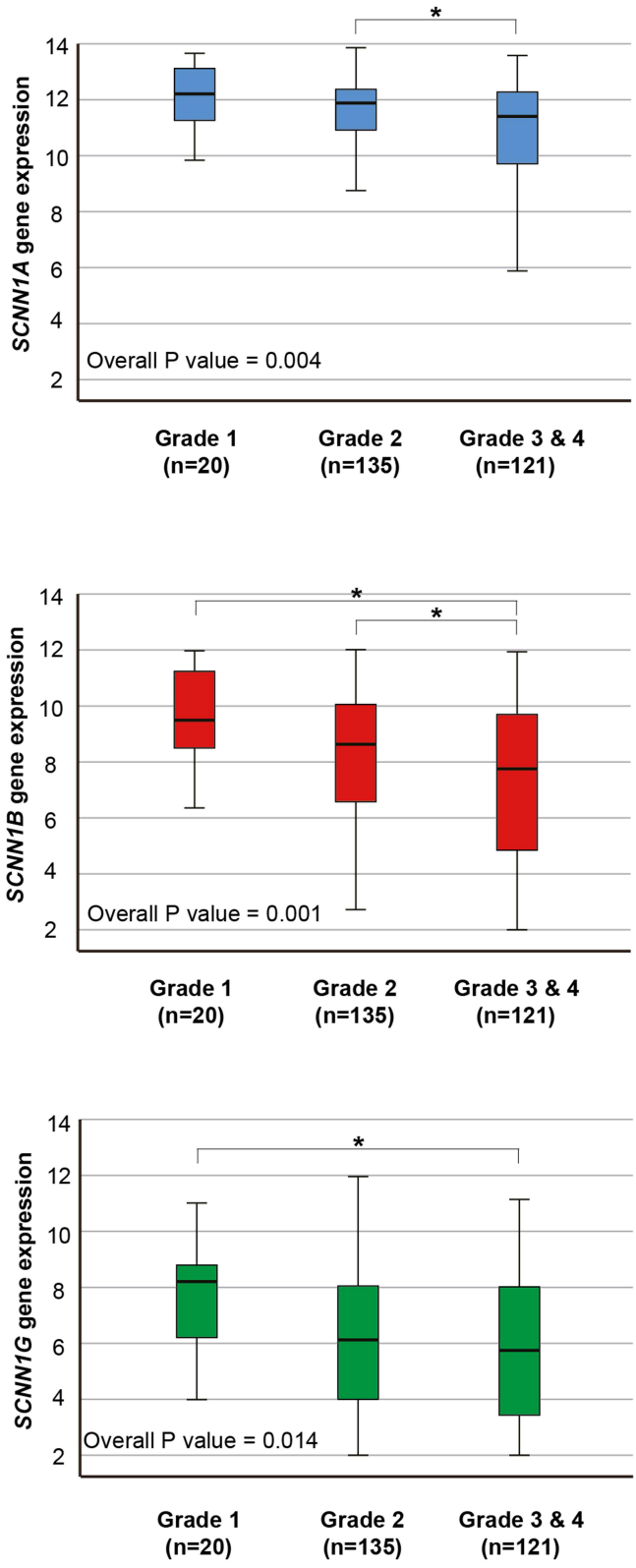

Figure 4 Box plots presenting relative expression levels of *SCNN1A*, *SCNN1B*, and *SCNN1G* in cervical cancer patients according to histologic grade. *Bonferroni's post hoc test P < 0.025.

Table 3 Correlation of *SCNN1A, SCNN1B*, and *SCNN1G* mRNA Expression and Clinicopathologic Features of Cervical Cancer Patients

Parameters		mRNA Expression Levels		Chi-square value	P value
		Higher/Higher/Higher (N=83)	Lower/Lower/Lower (N=84)		
Age (years)	<60	67	71	0.420	0.517
	≥60	16	13		
	Null	0	0		
Clinical stage	≤ Ib1	38	33	0.844	0.358
	≥ Ib2	44	51		
	Null	1	0		
Histologic grade	G1, G2	52	34	7.871	0.005
	G3, G4	23	39		
	Null	8	11		
Lympho-vascular invasion	No	19	21	3.012	0.083
	Yes	31	16		
	Null	33	47		
Primary therapy outcome	CR, PR, SD	58	55	0.571	0.450
	PD	3	5		
	Null	22	24		
New tumor after primary therapy	No	62	60	0.073	0.786
	Yes	10	11		
	Null	11	13		
Personal tumor status	Tumor free	61	54	1.682	0.195
	With tumor	16	23		
	Null	6	7		

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

were positively correlated with each other, and the genes were functionally enriched in maintaining sodium and water homeostasis. The logFC analysis of gene expression between normal and tumor tissues from GSE63514 and GSE6791 datasets showed overexpression of *SCNN1A, SCNN1B*, and *SCNN1G* in normal tissues than in tumor tissues. Survival analyses showed that simultaneous overexpression of all three genes was associated with better OS in cervical cancer patients. Likewise, higher expression of *SCNN1B* and *SCNN1G* was associated with better OS, while *SCNN1A* expression had no association with survival. Interestingly, the expression levels of *SCNN1B* and *SCNN1G* were more positively correlated with each other than with that of *SCNN1A*. *SCNN1B* and *SCNN1G* are functionally enriched in excretion (GO: 0007588), while *SCNN1A* is not involved in (Table 2). However, further studies are needed to determine whether the result that overexpression of *SCNN1B* and *SCNN1G* is associated with better OS is associated with excretion.

Table 4 Correlation Between Histologic Grade and Each mRNA Expression Level of *SCNN1A, SCNN1B*, and *SCNN1G*

Gene	Pearson's Correlation Coefficient Analysis		Histologic Grade	Mean mRNA Expression
	Coefficient (r)	P value		
SCNN1A	−0.204	0.001	G1 (n=20)	12.100375
			G2 (n=135)	11.350941
			G3 & G4 (n=121)	10.828838
SCNN1B	−0.245	0.0001	G1 (n=20)	9.512410
			G2 (n=135)	8.041384
			G3 & G4 (n=121)	7.022166
SCNN1G	−0.142	0.018	G1 (n=20)	7.639425
			G2 (n=135)	5.880453
			G3 & G4 (n=121)	5.632390

Furthermore, the analyses of relationship between expression levels of *SCNN1A, SCNN1B*, and *SCNN1G* and clinicopathologic features of cervical cancer patients showed that overexpression of all three genes was associated with lower histologic grade of tumor. Moreover, the mean mRNA expression level of each gene was negatively correlated with the histologic grade of tumor. Taken together, these results demonstrate that overexpression of *SCNN1A, SCNN1B*, and *SCNN1G* may be a potential biomarker for predicting better prognosis of cervical cancer patients.

Accumulating evidence suggests that ENaC-encoding genes are oncogenes and ENaC and ENaC-encoding genes are potential therapeutic targets. For example, Ware et al suggested that ENaC is associated with cancer cell proliferation in breast cancer and may be a potential therapeutic target in breast cancer.[27] He et al suggested ENaC as a therapeutic target for pulmonary neuroendocrine tumors.[28] Conversely, Qian et al reported that SCNN1B suppresses gastric cancer growth and metastasis.[29] Similarly, our finding suggests that ENaC and ENaC-encoding genes are associated with lower histologic grade of tumor and better survival. Further studies are required to investigate the relationship between ENaC and cervical cancer and verify the application of ENaC as a therapeutic target and prognostic values of *SCNN1A, SCNN1B*, and *SCNN1G* genes in cervical cancer patients.

Conclusion

This study identified that *SCNN1A, SCNN1B*, and *SCNN1G* genes, which encode ENaC, are associated with lower histologic grade and better survival in cervical cancer patients. We suggested for the first time that these genes could be used as biological markers to better predict survival outcomes in cervical cancer patients.

Data Sharing Statement

The datasets generated in the present study are available from the corresponding authors upon reasonable request. The datasets analyzed during the present study are available from The Cancer Genome Atlas (https://www.cancer.gov/tcga), the UCSC Xena (https://xena.ucsc.edu), and the GEO databases (http://www.ncbi.nlm.nih.gov/geo/).

Ethical Statement

All samples of GSE6791 were collected with patient consent under approval from institutional review boards from the University of Iowa and Harvard School of Public Health, the National Disease Research Interchange, and the Gynecologic Oncology Group. All the samples of GSE63514 were obtained with patient consent and approval of the Human Subject Research Institutional Review Boards at the University of Wisconsin–Madison, the National Cancer Institute, and the University of Oklahoma Health Sciences Center, women were recruited into the Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED). Moreover, this study met the publication guidelines provided by TCGA (http://www.cancer.gov/about-nci/organization/ccg/research/structrual-genomics/tcga/using-tcga/citing-tcga). The use of the evaluated publicly available data was approved by the Institutional Review Board of Keimyung University Dongsan Medical

Center on 25 November 2021 (IRB No. 2021-11-058). The study was conducted according to the guidelines of the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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