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Identification of novel diagnostic markers for sinonasal undifferentiated carcinoma

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Abstract

Background: Sinonasal undifferentiated carcinoma (SNUC) is a rare, highly aggressive cancer. It is often difficult to determine whether SNUC is a distinct pathologic entity with poorly differentiated neuroendocrine features or it represents an undifferentiated tumor of squamous lineage. Also, reliable histopathologic markers that distinguish SNUC from poorly differentiated sinonasal squamous cell carcinoma (SNSCC) are lacking. Therefore, identification of new diagnostic molecular markers for SNUC is needed.

Methods: Treatment-naïve tumor specimens obtained from 15 SNUC and 6 SNSCC patients were used. Gene expression analysis was performed using an oncology panel.

Results: An unsupervised cluster analysis divided the patients into the one with only SNUCs and the one with mainly SNSCCs. Of 132 differentially expressed genes, 7 genes completely distinguished SNUCs from SNSCCs. SNUCs were enriched in sets of genes related to DNA repair, synthesis/replication, and cell division.

Conclusions: Our study identified new diagnostic markers and potential therapeutic targets for SNUC.

KEYWORDS

comprehensive gene expression study, diagnostic markers, sinonasal squamous cell carcinoma, sinonasal undifferentiated carcinoma, therapeutic targets

1 | INTRODUCTION

Sinonasal undifferentiated carcinoma (SNUC) is a rare, highly aggressive cancer. Initially described by Frierson et al,[1] the latest definition of SNUC by the World Health Organization is "undifferentiated carcinoma of the sinonasal tract without glandular or squamous features and not otherwise classifiable."[2] In general, SNUCs present as large tumors that involve multiple sinonasal structures and often extend into the orbit or cranial cavity. These tumors can metastasize to the cervical lymph nodes, lungs, bone, brain, and liver.[3–6] Treatment of SNUC includes aggressive multimodal therapy with radiotherapy, chemotherapy, and in some instances, surgery.[4,6–8] Despite aggressive management of SNUC, the prognosis remains poor, with a median survival time after diagnosis of 23.5 months in the Unites States.[9] Thus, development of new therapies is essential to improving the survival of patients with SNUC.

However, little is known about the histogenesis and molecular biology of SNUC. It remains unclear whether SNUC is a distinct pathologic entity with poorly differentiated neuroendocrine features or an undifferentiated tumor of squamous lineage.[10] Moreover, reliable histopathologic markers that distinguish SNUC from undifferentiated sinonasal squamous cell carcinoma (SNSCC) are lacking. Distinguishing between SNSCC and

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SNUC has significant clinical importance because the prognosis and treatment strategies are different. Generally SNUC is viewed to have worse outcome than SNSCC with higher rates of distant metastasis and worse survival. Therapeutic strategies are also different with primary surgery and adjuvant radiation being the mainstay of treatment for SNSCC, while SNUC is usually treated with trimodality therapy frequently incorporating induction chemotherapy and concurrent chemoradiation in the overall treatment strategy. Another important aspect of distinguishing SNUC from SNSCC is eligibility for clinical trials of these rare diseases.[11] Therefore, new diagnostic molecular markers for SNUC are needed.

The most problematic part of molecular profiling in studying SNUC is a lack of surgical specimens. Because of the rarity of this tumor, tissue acquisition for comprehensive gene expression/marker studies is quite challenging, and most of the available biologic materials are formalin-fixed paraffin-embedded (FFPE) specimens, which had not been previously suitable for genomic characterization. To identify gene expression signature and specific diagnostic markers for SNUC that distinguish it from SNSCC, we performed comprehensive gene expression analysis of tumor specimens obtained from treatment-naïve SNUC and SNSCC specimens. To that end, we employed the HTG EdgeSeq system (HTG Molecular Diagnostics, Tucson, Arizona), which enabled us to use only small FFPE specimens to perform expression analysis.

2 | PATIENTS AND METHODS

2.1 | Patients and specimens

For this retrospective gene expression analysis, 16 tumor specimens obtained from 15 treatment-naïve SNUC patients and 6 tumor specimens obtained from 6 treatment-naïve SNSCC patients via biopsy or surgery performed at The University of Texas MD Anderson Cancer Center were examined. All of the specimens were FFPE and were re-reviewed by a single head and neck pathologist (D.B.). Two specimens (labeled as SNUC 21 [or biopsy Part A1] and SNUC 22 [or biopsy Part B]) obtained in a single biopsy for one patient were included to assess the reliability of the RNA expression analysis system we employed (see below). Patient data were collected from an institutional database. Patient demographic and clinical characteristics are listed in Table 1. MD Anderson Institutional Review Board approval was obtained prior to the start of the study (Protocols LAB05-0228, PA12-0995, and RAR004-0636) and all patients provided written informed consent.

2.2 | RNA expression analysis

Lysates were prepared from SNUC and SNSCC specimens using HTG Lysis Buffer and run on an HTG EdgeSeq processor using an HTG EdgeSeq Oncology Biomarker Panel with 2560 oncology-related genes, in which an excess of nuclease protection probes (NPPs) complementary to each mRNA hybridize to their targets. S1 nuclease was then removed from unhybridized probes and RNA, leaving only NPPs hybridized to their targets at a 1:1 ratio. To prepare a library, samples were individually barcoded using a polymerase chain reaction to add adapters and molecular barcodes and individually purified using a Kapa

TABLE 1 Demographic and clinical characteristics of the study patients

Characteristics		SNSCC	SNUC	*P*-value
Sex	Female	2	6	1.000
	Male	4	9	
Race	Asian	0	2	.480
	Black	0	1	
	Latin	2	1	
	White	4	11	
Primary tumor site	Ethmoid sinus	0	6	.100
	Frontal sinus	1	1	
	Maxillary sinus	4	3	
	Nasal cavity	1	5	
T classification	T3	1	0	.285
	T4	5	15	
N classification	N+	1	3	1.000
	N0	5	12	
M classification	M0	6	13	1.000
	M1	0	2	
Clinical stage	IVc	0	2	1.000
	IVa	4	8	
	IVb	2	5	
Carcinogen exposure	No	6	13	.490
	Yes (lead)	0	1	
	Yes (radiation exposure)	0	1	
Smoking status	Current	1	0	.072
	Former	4	5	
	Never	1	10	
Alcohol status	Current	3	4	.698
	Former	1	4	
	Never	2	7	
Tumor recurrence	No	5	6	.148
	Yes	1	9	

Abbreviations: SNSCC, sinonasal squamous cell carcinoma; SNUC, sinonasal undifferentiated carcinoma.

Library Quantification Kit (Kapa Biosystems, Wilmington, Massachusetts). The library was sequenced on an Ion Torrent PGM Sequencer (Thermo Fisher Scientific, Waltham, Massachusetts) for quantification. The sequence data were processed and reported by the HTG EdgeSeq parser software.

2.3 | Statistical methods and gene set enrichment analysis

Differentially expressed genes (DEGs) between SNUC and SNSCC cases were assessed using a false-discovery rate (FDR) technique[12] considering a significance level of 0.05. FDR calculations, hierarchical cluster, principal component, and survival analyses were performed using the JMP Pro software program (version 12.1.0; SAS Institute, Cary, North Carolina). For hierarchical cluster analysis of DEG between SNUC and SNSCC groups, clustering distances were determined using Ward's minimum variance method. Principal component analysis was performed with the default option. Differences in survival curves for the study patients in a Kaplan-Meier plot were determined using a log-rank test. Receiver operating characteristic (ROC) analysis was used to assess the discriminatory power between SNUC and SNSCC specimens for selected genes. Pearson's correlation analyses of gene expression levels in technical replicates (sample SNUC21 and SNUC22) was performed using the Prism 6 software program (GraphPad Software, La Jolla, California). Biological processes associated with DEGs were assessed via gene ontology (GO) analysis using the gene set enrichment analysis (GSEA) software (version 3.0) with the C5.BP.v6.1 gene set, considering a significance level of 0.05.

3 | RESULTS

3.1 | Comparison of the demographics of the SNUC and SNSCC patients

We first examined whether the demographics differed between the SNUC and SNSCC patients. We did not observe any statistically significant demographic differences between the two groups. The median follow-up times from presentation at MD Anderson to death or last contact were 30.8 months (range, 11.5-33.8 months) in the SNUC patients and 39.8 months (range, 6.2-207.7 months) in the SNSCC patients.

3.2 | Unsupervised clustering of the gene expression in SNUC and SNSCC specimens

To evaluate the reliability of the HTG EdgeSeq Oncology Biomarker Panel, we compared the gene expression between two biopsy specimens obtained from a single patient in one procedure (SNUC 21 and SNUC 22) (Figure 1A). We observed a high linear correlation between the two specimens (Pearson's correlation coefficient, 0.96; $P = .0001$), indicating superb reliability and sensitivity of the panel. We then performed unsupervised cluster analysis to determine whether SNUC and SNSCC can be differentiated based on their gene expression patterns obtained from the HTG EdgeSeq Oncology Biomarker Panel. This analysis divided the tumor specimens into two groups; the upper group clustered SNUC specimens only (SNUC cluster), and the lower group clustered mainly SNSCC specimens (SNSCC cluster) (Figure 1B).

3.3 | DEGs between SNUC and SNSCC specimens

To identify molecular markers that can distinguish SNUC from SNSCC, we determined DEGs between these two tumor types by setting a FDR less than 0.05. This rate cutoff identified a set of 132 DEGs in SNUC and SNSCC specimens (File 1). Hierarchical cluster analysis performed with these 132 genes perfectly distinguished SNUC from SNSCC (Figure 2A). Principal component analysis (PCA) further confirmed the difference between the two tumor types (Figure 2B). Of note, theses 132 DEGs further divided the SNUC specimens into two subgroups (SNUC groups 1 and 2: shown in gray and yellow, respectively, in Figure 2A). PCA also demonstrated complete separation between these two subgroups (Figure 2C). SNUC group 2 seemed to have an intermediate pattern of gene expression between SNUC and SNSCC specimens. We saw no difference in the 5-year survival rate between the two patient groups ($P = .674$ [log-rank test]). Of the 132 DEGs, *CLCA2* had the lowest FDR (<0.001), and its expression accurately discriminated SNUC from SNSCC (area under the curve [AUC] = 1.0) (Figure 3). Additionally, expression of six other genes (*ARID2*, *MAP1LC3A*, *SMAD4*, *HELLS*, *MAPKAPK5-AS1*, and *KRT16*) completely distinguished SNUC from SNSCC (AUC = 1.0) (Figure 3).

3.4 | Distinct molecular characteristics of SNUC and SNSCC

To identify distinct molecular characteristics of SNUC and SNSCC, we performed GSEA of the 132 DEGs. This analysis is a computational method that determines whether an a priori defined set of genes differs between two biological states in a statistically significant manner.[13,14] GO analysis results identified molecular functions enriched by significantly expressed genes in SNUC and SNSCC specimens (Tables 2 and 3, respectively). The enriched genes in SNUCs were significantly related to several molecular functions: DNA repair, synthesis, and replication; protein modification; and cell division. In comparison, SNSCCs exhibited enrichment of inflammation-related genes.

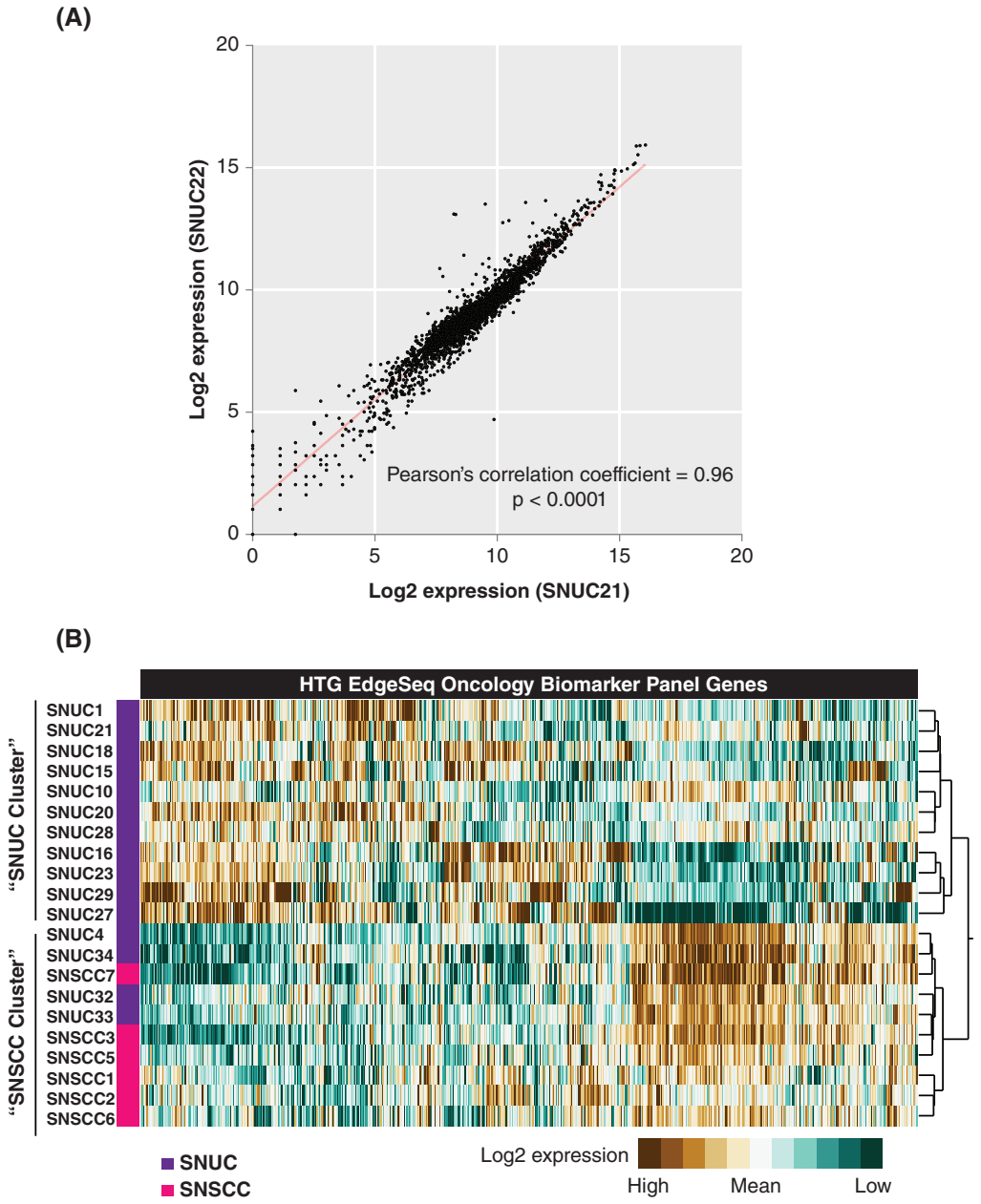

FIGURE 1 Gene expression levels in sinonasal undifferentiated carcinoma (SNUC) and sinonasal squamous cell carcinoma (SNSCC) specimens obtained from treatment-naïve patients. A, Comparison of the gene expression levels between two biopsy specimens obtained in the same procedure from the same patient (SNUC 21 and SNUC 22). High linear correlation of the two specimens indicating great reliability and sensitivity of the HTG EdgeSeq system is shown. B, Unsupervised cluster analysis of the expression of 2560 genes in tumor specimens from 15 treatment-naïve SNUC and 6 treatment-naïve SNSCC patients. The majority of SNUC specimens were clustered in the top half of the map whereas mainly SNSCC specimens were clustered in the bottom half, indicating a distinct gene expression profile between these groups

4 | DISCUSSION

The aim of this study was to identify the gene expression signature in SNUC. We succeeded in discovering distinct markers and molecular characteristics of SNUC.

Because of its rarity, molecular profiling of SNUC has been challenging. Thus, we chose to use the HTG EdgeSeq system, which enabled us to analyze the gene expression profiles in FFPE specimens and even core needle biopsy specimens.[15] Comparison of the gene expression patterns between the two biopsy specimens obtained from the same patient in the same procedure demonstrated a high linear correlation between the two specimens, indicating a high level of reliability of this system.

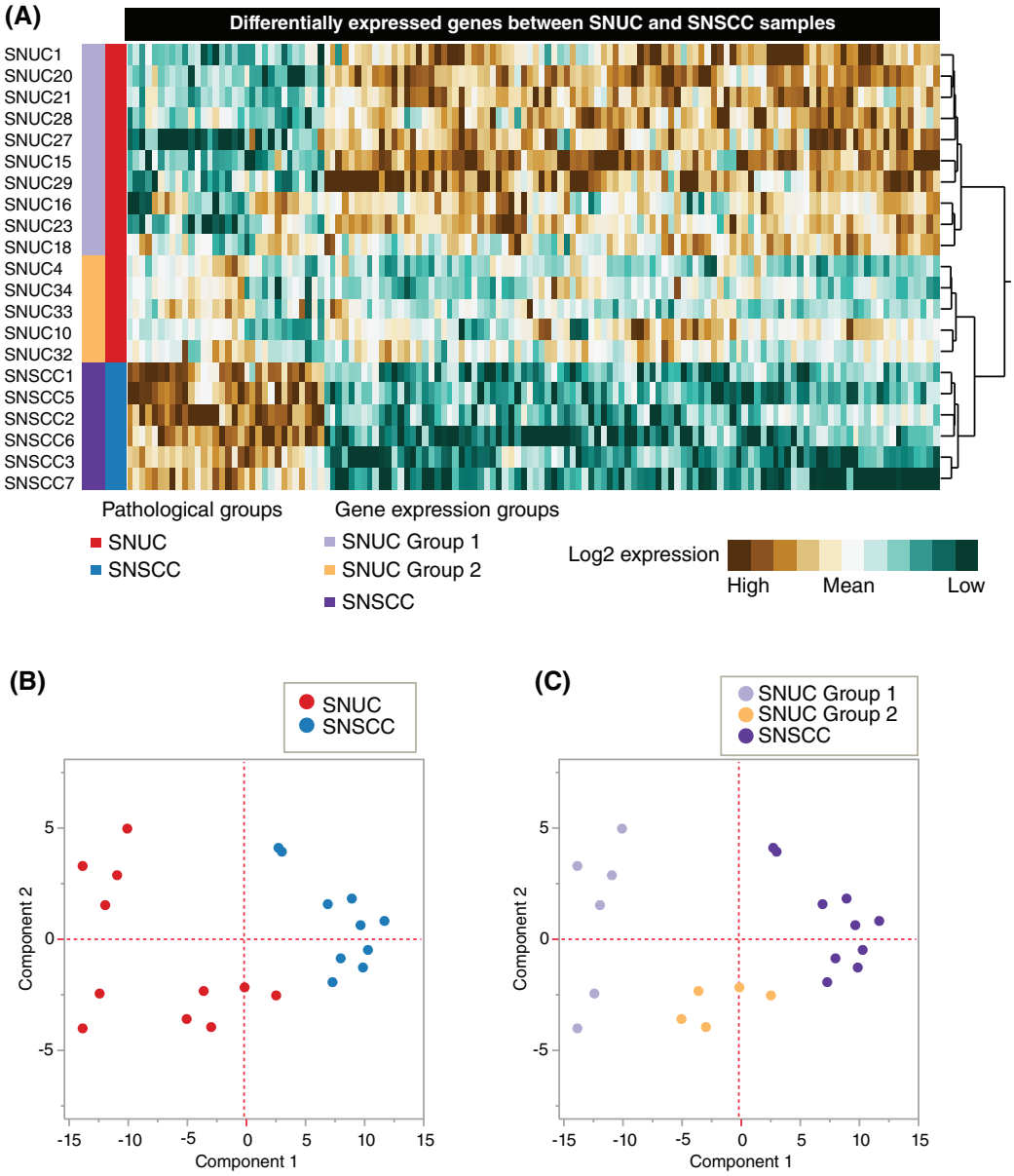

FIGURE 2 Differentially expressed genes (DEGs) between sinonasal undifferentiated carcinoma (SNUC) and sinonasal squamous cell carcinoma (SNSCC) specimens. One hundred thirty-two DEGs between SNUC and SNSCC specimens were analyzed. A, Hierarchical cluster analysis performed with these 132 genes indicated a clear distinct gene expression profile between SNUC and SNSCC. Also, it indicated two subgroups among SNUC specimens. B, Principal component analysis with the 132 genes confirmed the complete distinction between SNUC and SNSCC specimens, and C, the separation of the SNUC specimens into two subgroups (SNUC groups 1 and 2)

Whether SNUC is a distinct pathologic entity with poorly differentiated neuroendocrine features or an undifferentiated tumor of squamous lineage has been controversial.[10] To answer this question, we performed unsupervised cluster analysis of gene expression patterns in SNUC and SNSCC specimens from treatment-naïve patients. Interestingly, the specimens were clustered into two groups: one had SNUC specimens only and the other mainly SNSCC specimens. This indicated that SNUC is independent of SNSCC rather than a type of SNSCC. Including other neuroendocrine tumors, such as sinonasal neuroendocrine carcinoma, sinonasal small cell carcinoma, and olfactory neuroblastoma, in such cluster analysis will be our next step in determining which of the categories described above SNUC belongs in.

Of the seven identified genes (*CLCA2*, *ARID2*, *MAP1LC3A*, *SMAD4*, *HELLS*, *MAPKAPK5-AS1*, and *KRT16*) whose expression discriminated SNUC from SNSCC, *CLCA2* was the most differentially expressed in the two groups. The protein encoded by this gene belongs to the calcium-activated chloride channel regulator family of proteins. Furthermore, *CLCA2* is involved in

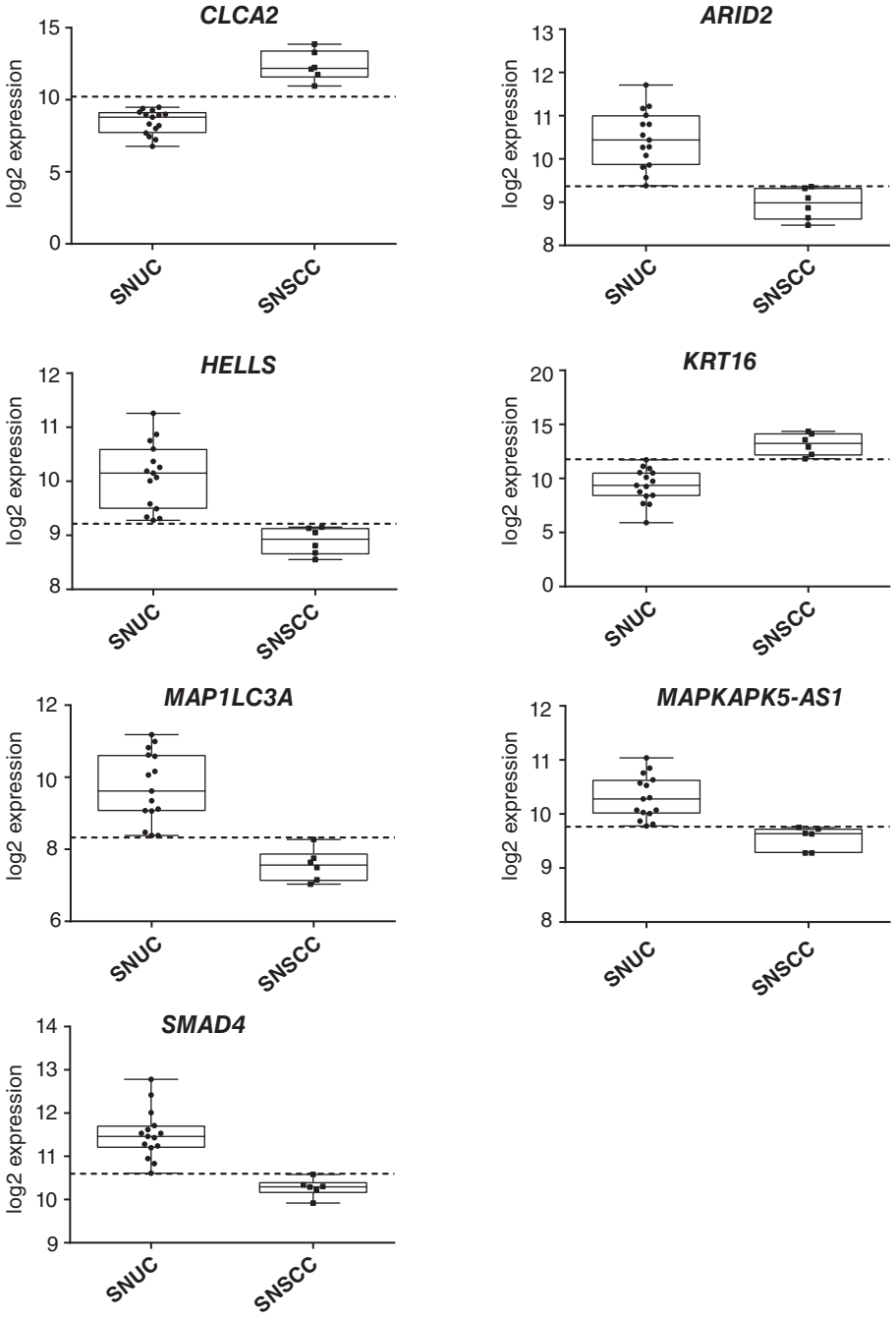

FIGURE 3 Seven genes completely distinguished sinonasal undifferentiated carcinoma (SNUC) from sinonasal squamous cell carcinoma (SNSCC). Of the 132 differentially expressed genes we identified, *CLCA2*, *ARID2*, *MAP1LC3A*, *SMAD4*, *HELLS*, *MAPKAPK5-AS1*, and *KRT16* completely distinguished SNUC and SNSCC specimens. The dotted lines in the graphs indicate 100% sensitivity and specificity

the p53 tumor suppression network and has a significant effect on cell migration and invasion in different cell types.[16] Another study demonstrated that expression of this gene is a characteristic of epithelial differentiation, whereas induction of epithelial-to-mesenchymal transition sharply reduces CLCA2 expression.[17] Taken together, low expression of *CLCA2* in SNUCs may give this cancer its invasive nature. We aim to develop immunohistochemical staining for CLCA2 to determine whether this gene product can be used as a pathologic diagnostic marker to distinguish SNUC from SNSCC.

To understand the biologic features of SNUC, we performed GSEA of SNUC and SNSCC specimens. Of 37 gene ontologies enriched in SNUCs, most of them were related to DNA repair, cell-cycle progression, mitosis, DNA synthesis, and protein modification. The mitotic rate in SNUCs is known to be very high.[10,18] Therefore, that several cell cycle-related ontologies were upregulated in SNUC specimens is reasonable. Human cells have five major DNA damage repair (DDR) pathways—base excision repair, homologous recombination repair, nonhomologous end-joining, nucleotide excision repair, and mismatch repair—and different kinds of DNA damage induce responses via different repair mechanisms and signaling pathways.[19,20] Also, the cell cycle has three checkpoints—G1/S, S-phase, and G2/M—the last of which is the last opportunity for

TABLE 2 Molecular functions related to enriched genes in sinonasal undifferentiated carcinoma specimens

GO term	FDR *q*-value
GO protein sumoylation	0.009414
GO double-strand break repair	0.015648
GO peptidyl lysine modification	0.016054
GO chromosome organization	0.016557
GO DNA metabolic process	0.017497
GO negative regulation of gene expression epigenetic	0.017541
GO DNA repair	0.019363
GO DNA biosynthetic process	0.021712
GO cell cycle	0.029197
GO organelle fission	0.031718
GO meiotic cell cycle	0.032063
GO DNA recombination	0.032416
GO cell division	0.032791
GO regulation of telomere maintenance	0.033915
GO chromatin organization	0.034102
GO reciprocal DNA recombination	0.034658
GO DNA conformation change	0.035173
GO multicellular organism growth	0.035749
GO regulation of DNA repair	0.036538
GO protein modification by small protein conjugation or removal	0.037494
GO mitotic cell cycle	0.037883
GO response to lithium ion	0.038704
GO chromatin modification	0.039172
GO positive regulation of phosphatidylinositol 3 kinase signaling	0.039217
GO nucleotide excision repair	0.039315
GO meiosis I	0.039367
GO nonrecombinational repair	0.039597
GO cell cycle process	0.039825
GO DNA replication	0.039898
GO meiotic chromosome segregation	0.040046
GO recombinational repair	0.040459
GO positive regulation of telomere maintenance	0.040666
GO chromatin assembly or disassembly	0.040857
GO DNA-dependent DNA replication	0.041847
GO covalent chromatin modification	0.043334
GO protein stabilization	0.047291
GO chromosome organization involved in meiotic cell cycle	0.047945

Abbreviations: FDR, false-discovery rate; GO, gene ontology.

TABLE 3 Molecular functions related to enriched genes in sinonasal squamous cell carcinoma specimens

GO term	FDR *q*-value
GO chemokine-mediated signaling pathway	0.002122832
GO drug metabolic process	0.018339852
GO fatty acid derivative metabolic process	0.021179197
GO positive regulation of inflammatory response	0.036304154
GO regulation of interferon gamma production	0.037253875
GO lymphocyte migration	0.044616590

Abbreviations: FDR, false-discovery rate; GO, gene ontology.

repair of DNA damage. If cells enter mitosis, unrepaired double-strand breaks and under replicated DNA may result in mitotic catastrophe and cell death.[21] This indicates that inhibiting the function of some DDR factors in the G2/M checkpoint may induce mitotic catastrophe and cell death in SNUCs.

In summary, SNUC has a different gene expression spectrum from that of SNSCC and significant signature signaling pathways. This is the first report of a comprehensive gene expression study of SNUC, and our findings provide promising leads for the definitive molecular diagnosis SNUC.

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REFERENCES

1. Frierson HF Jr, Mills SE, Fechner RE, Taxy JB, Levine PA. Sinonasal undifferentiated carcinoma. An aggressive neoplasm derived from schneiderian epithelium and distinct from olfactory neuroblastoma. *Am J Surg Pathol*. 1986;10(11):771-779.
2. Lewis JS, Bishop JA, Gillison M, Westra WH, Yarbrough WG. Tumors of the nasal cavity, paranasal sinuses and skull base-Sinonasal undifferentiated carcinoma. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, eds. *WHO Classification of Head and Neck Tumors*. 4th ed. Lyon: International Agency for Research on Cancer; 2017:18-20.

3. Cerilli LA, Holst VA, Brandwein MS, Stoler MH, Mills SE. Sinonasal undifferentiated carcinoma: immunohistochemical profile and lack of EBV association. *Am J Surg Pathol*. 2001;25(2):156-163.
4. Ejaz A, Wenig BM. Sinonasal undifferentiated carcinoma: clinical and pathologic features and a discussion on classification, cellular differentiation, and differential diagnosis. *Adv Anat Pathol*. 2005; 12(3):134-143.
5. Ghosh S, Weiss M, Streeter O, Sinha U, Commins D, Chen TC. Drop metastasis from sinonasal undifferentiated carcinoma: clinical implications. *Spine (Phila Pa 1976)*. 2001;26(13):1486-1491.
6. Mendenhall WM, Mendenhall CM, Riggs CE Jr, Villaret DB, Mendenhall NP. Sinonasal undifferentiated carcinoma. *Am J Clin Oncol*. 2006;29(1):27-31.
7. Tanzler ED, Morris CG, Orlando CA, Werning JW, Mendenhall WM. Management of sinonasal undifferentiated carcinoma. *Head Neck*. 2008;30(5):595-599.
8. Smith SR, Som P, Fahmy A, Lawson W, Sacks S, Brandwein M. A clinicopathological study of sinonasal neuroendocrine carcinoma and sinonasal undifferentiated carcinoma. *Laryngoscope*. 2000;110(10 Pt 1):1617-1622.
9. Chambers KJ, Lehmann AE, Remenschneider A, et al. Incidence and survival patterns of sinonasal undifferentiated carcinoma in the United States. *J Neurol Surg Part B, Skull Base*. 2015;76(2): 94-100.
10. Bell D, Hanna EY, Weber RS, et al. Neuroendocrine neoplasms of the sinonasal region. *Head Neck*. 2016;38(suppl 1):E2259-E2266.
11. Amit M, Abdelmeguid AS, Watcherporn T, et al. Induction chemotherapy response as a guide for treatment optimization in Sinonasal undifferentiated carcinoma. *J Clin Oncol*. 2019;37(6):504-512.
12. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B (Methodological)*. 1995;57(1):289-300.
13. Subramanian A, Tamayo P, Mootha VK, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci U S A*. 2005;102(43): 15545-15550.
14. Mootha VK, Lindgren CM, Eriksson K-F, et al. PGC-1α-responsive genes involved in oxidative phosphorylation are coordinately down-regulated in human diabetes. *Nat Genet*. 2003;34:267-273.
15. Girard L, Rodriguez-Canales J, Behrens C, et al. An expression signature as an aid to the histologic classification of non-small cell lung cancer. *Clin Cancer Res*. 2016;22(19):4880-4889.
16. Sasaki Y, Koyama R, Maruyama R, et al. CLCA2, a target of the p53 family, negatively regulates cancer cell migration and invasion. *Cancer Biol Ther*. 2012;13(14):1512-1521.
17. Walia V, Yu Y, Cao D, et al. Loss of breast epithelial marker hCLCA2 promotes epithelial-to-mesenchymal transition and indicates higher risk of metastasis. *Oncogene*. 2012;31(17):2237-2246.
18. Mills SE, Fechner RE. "Undifferentiated" neoplasms of the sinonasal region: differential diagnosis based on clinical, light microscopic, immunohistochemical, and ultrastructural features. *Semin Diagn Pathol*. 1989;6(4):316-328.
19. O'Connor MJ. Targeting the DNA damage response in cancer. *Mol Cell*. 2015;60(4):547-560.
20. Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. *Nature*. 2001;411(6835):366-374.
21. Castedo M, Perfettini JL, Roumier T, Andreau K, Medema R, Kroemer G. Cell death by mitotic catastrophe: a molecular definition. *Oncogene*. 2004;23(16):2825-2837.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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