# Distinct Gene Mutations Are Associated With Clinicopathologic Features in Urachal Carcinoma

## An Analysis of 30 Cases by Next-Generation Sequencing

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## ABSTRACT

**Objectives:** To investigate the gene mutational profile of urachal carcinoma in correlation with its clinicopathologic features.

**Methods:** We analyzed genetic mutations in 30 cases of urachal carcinoma by next-generation sequencing (NGS) test. Histologic slides and clinical data were reviewed.

**Results:** The patients included 21 men and 9 women, with a mean age of 53 years (range, 24-75 years). The urachal carcinomas included mucinous (11), enteric (10), signet ring cell (8), and high-grade neuroendocrine (1) subtypes. Targeted NGS analysis demonstrated genetic mutations in all the urachal tumors (mean, 2; range, 1-4). *TP53* was the most mutated gene (25), followed by *KRAS* (9) and *GNAS* (8) genes. *TP53* mutations were more common in the signet ring cell subtype (7/8), and *GNAS* mutations were present only in the mucinous (5/11) and signet ring cell subtypes (3/8) but not in the enteric subtype (0/10). *KRAS* mutations were significantly associated with cancer stage IV ($P = .02$) and younger patient age ($P = .046$). Furthermore, the presence of *KRAS* mutations in urachal carcinoma portended a poorer overall survival ($P = .006$).

**Conclusions:** Urachal carcinoma demonstrates frequent gene mutations that are associated with distinct clinicopathologic features. Gene mutation may underlie the development and progression of this aggressive disease.

## INTRODUCTION

Urachal carcinoma is a rare malignant neoplasm that arises from the urachal remnant.[1-7] The urachus is a vestigial structure that connects the urinary bladder to the allantois during embryonal development, facilitating liquid waste discharge and gas exchange.[2,6] After birth, the urachus is usually obliterated and becomes a fibrous cord called the median umbilical ligament; however, approximately 30% of adults have a urachal remnant, a tubular or cystic

## KEY POINTS

- Urachal carcinoma demonstrates frequent gene mutations, with the *TP53*, *KRAS*, and *GNAS* genes being the most mutated. Gene mutations are associated with distinct clinicopathologic features.
- *TP53* mutations are most frequent in the signet ring cell subtype, while *GNAS* mutations are associated with mucinous and signet ring cell subtypes.
- *KRAS* mutations are more common in high-stage cancers and young patients. The presence of *KRAS* mutations in urachal carcinoma portends a poor clinical outcome.

## KEY WORDS

Urachal carcinoma; Next-generation sequencing; Gene mutations; *TP53*; *KRAS*; *GNAS*

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structure in the bladder dome or elsewhere along the midline of the anterior wall.[1,2] Although the urachal remnant is usually lined by urothelium, most urachal carcinomas are composed of adenocarcinoma, including mucinous, enteric, signet ring cell, and not otherwise specified (NOS) subtypes.[7] Other carcinomas, such as urothelial carcinoma, squamous carcinoma, and neuroendocrine carcinoma, may also occur in rare instances.[8,9] The histologic divergence between the urachal remnant and urachal carcinoma is likely due to the intestinal metaplastic change of the urachal epithelium.[2,8] Other researchers think that primitive colonic remnants (cloacal) may also contribute to this morphologic discrepancy, since the cloaca is in close proximity to the urachus during embryonal development.[8,10]

Urachal carcinoma is an aggressive disease that frequently spreads to the bladder and other organs.[1-7] Several staging systems have been proposed for urachal carcinoma, and the Sheldon system, which is endorsed by the World Health Organization, is the most widely used.[1,2,4,7] Over 90% of urachal carcinomas are diagnosed at advanced stages (Sheldon stage III or IV), and about 21% of patients have developed distant metastasis at initial presentation.[11] The overall prognosis is poor, and the average 5-year cancer-specific survival rate is 64.4%.[11] At advanced stages, it is difficult, if not impossible, to eradicate the disease by surgery alone, and systemic therapy is often part of the treatment regimen. As only 30% to 40% of patients experience a response to conventional chemotherapy, targeted therapy based on the molecular signature of urachal carcinoma is needed for this aggressive disease.[6,11-13] A better understanding of genetic mutations in urachal carcinoma may lead to more effective targeted therapy. To elucidate the mutational profile of urachal carcinoma, we performed a next-generation sequencing (NGS) analysis in a large cohort of urachal carcinomas from a single institution in correlation with the clinicopathologic features.

## MATERIALS AND METHODS

This study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center (Houston, TX). We retrospectively searched the pathology files at MD Anderson from 2008 to 2020 and identified 30 patients with urachal carcinoma whose tumor samples had undergone NGS.

Patients' H&E and immunohistochemical slides were reviewed to confirm the diagnosis in accordance with the histopathologic criteria set by the World Health Organization: the tumor was located at the dome or anterior wall of the bladder, the tumor predominantly involved the muscularis propria or perivesical soft tissue with the epicenter at the bladder wall, extensive cystitis cystica or cystitis glandularis was not present beyond the dome or anterior wall, and there was no known primary carcinoma of a similar histologic type at other anatomic locations.[7] The tumor clinical stage was based on the Sheldon staging system for urachal carcinoma: I, tumors were limited to the urachal mucosa; II, tumors invaded into but not beyond the urachal muscular layer; III, tumors extended to the bladder, abdominal wall, and other adjacent organs; and IV, tumors metastasized to the lymph nodes or other distant organs.[2,7] Data collected from the pathologic review and medical record included age, sex, and clinical presentation of symptoms; tumor size, location, stage, and histologic subtype; presence of signet ring cell features; and clinical outcome. Survival times were recorded from the date of initial diagnosis to the date of death or last follow-up.

NGS was performed on formalin-fixed, paraffin-embedded urachal carcinoma tissues and included a 50-Gene Somatic Mutation Analysis Panel (AmpliSeq Hotspot version 2) (n = 6), a 134-gene Solid Tumor Genomics Assay v1 (or Comprehensive Oncomine version 1) (n = 8), a 146-gene Solid Tumor Genomics Assay v3 (or Comprehensive Oncomine version 3) (n = 11), and a 409-Gene Somatic Mutation Analysis Panel (Ion AmpliSeq Comprehensive Cancer Panel) (n = 5) (Supplemental Tables 1-4; all supplemental materials can be found at *American Journal of Clinical Pathology* online).[14-16] All four NGS panels were purchased from Thermo Fisher Scientific. Our analysis was focused on the initial 50 key oncogenes and tumor suppressor genes, which were included in all the four test panels.

Statistics were calculated using standard methods and IBM SPSS version 24 for Windows (SPSS). The Kaplan-Meier method was used to plot survival curves, and differences between these curves were analyzed for significance using the log-rank test. The $\chi^2$ tests were performed to evaluate potential correlations between categorical groups. When categorical variables fell short of their expected count, the Fisher exact test was used. A $P$ value of less than .05 was considered statistically significant.

## RESULTS

### Pathologic Findings

The patients with urachal carcinoma included 21 men and 9 women with a mean age of 53 years (range, 24-75 years). Twenty-seven patients had gross or microscopic hematuria, and three had abdominal pain. One patient had mucosuria accompanied by hematuria. The tumors were located at the bladder dome (n = 23) or anterior wall (n = 7). The mean tumor size was 5.7 cm (range, 2.5-17 cm). The urachal carcinomas included mucinous (n = 11), enteric (n = 10), signet ring cell (n = 8), and high-grade neuroendocrine carcinoma (n = 1) subtypes. The mucinous subtype produced abundant extracellular mucin with floating tumor cells FIGURE 1A. The enteric subtype consisted of pseudostratified columnar cells with marked nuclear atypia and necrosis FIGURE 1B. The signet ring cell subtype was characterized by infiltrative tumor cells with a prominent intracellular mucinous vacuole that pushed the indented nucleus to the periphery FIGURE 1C. High-grade neuroendocrine carcinoma subtype was composed of solid sheets of poorly differentiated carcinoma FIGURE 1D and showed diffuse immunoreactivity for synaptophysin and chromogranin. In six cases, the urachal tumor showed mixed histologic subtypes, and the tumor classification was based on the predominant subtype, from which tumor sample was taken for the NGS test. At initial presentation, 17 patients had metastatic disease at stage IV using the Sheldon system TABLE 1. Thirteen patients had stage III, 10 of whom subsequently developed


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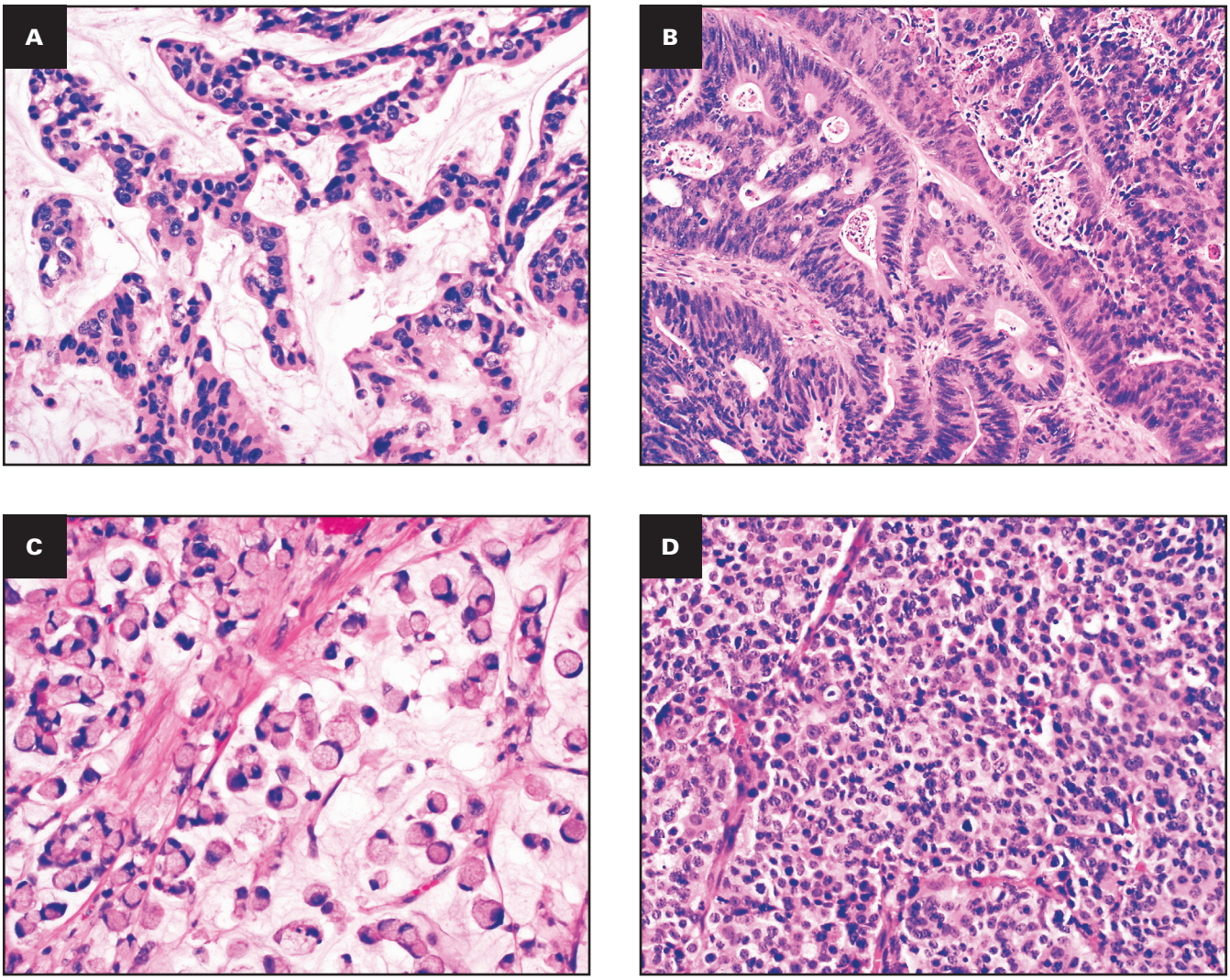


**FIGURE 1** Urachal carcinoma. **A**, Mucinous subtype. **B**, Enteric subtype. **C**, Signet ring cell subtype. **D**, High-grade neuroendocrine carcinoma subtype. (H&E, x200)

metastases in a mean of 2.8 years (range, 1.2-10.4 years). The metastatic sites included the lungs (n = 11), abdominal wall (not by direct extension) (n = 4), liver (n = 3), lymph nodes (n = 3), vertebra (n = 1), and vagina (n = 1).

### Molecular Data

NGS was performed on primary (n = 13) and metastatic (n = 17) tumors. All except for one tumor showed gene mutations that were covered by the 50-gene panel (Supplemental Table 1). The number of mutated genes per case ranged from 1 to 4 with a mean of 2.2 TABLE 1. The only tumor (case 11) with no gene mutations on the 50-gene panel was analyzed with a 409-gene panel, which demonstrated mutations in four other genes, including *GUCY1A2*, *MAPK2K1*, *MAPK2K2*, and *PTPRD* (Supplemental Table 4). Overall, *TP53* was the most frequently mutated gene (n = 25) FIGURE 2A, and one tumor harbored two mutations at different exons of the *TP53* gene (Supplemental Table 5). *TP53* mutation was found more often in the signet ring cell tumor subtype (7/8) than in the non–signet ring cell subtype ($P$ = .013). *KRAS* was the second most commonly mutated gene (n = 9) FIGURE 2B, followed by *GNAS* (n = 8) FIGURE 2C. Other commonly mutated genes included *SMAD4* (n = 7), *KIT* (n = 3), *MAP2K1* (n = 3), *ARID1A* (n = 3), *PIK3CA* (n = 3), *NOTCH1* (n = 2), *ATM* (n = 2), and *NF1* (n = 2). In addition, a number of other genes were also mutated TABLE 1. *GNAS* mutations were present only in the mucinous (5/11) or signet ring cell subtypes (3/8) but not in the enteric subtype (0/10). This difference was statistically significant ($P$ = .043). Interestingly, high-grade neuroendocrine carcinoma showed concurrent mutations in *TP53* and *RB1* genes, which were frequently present in lung and bladder small cell carcinomas.[17]

### Clinical Follow-up Findings

Follow-up information was available for all patients, with a mean follow-up time of 2.8 years (range, 0.4-10.4 years). Seventeen patients died of disease in a median of 1.6 years (range, 0.5-6.9 years). Ten patients were alive with disease (range, 0.4-10.4 years), and three patients were alive without evidence of disease (range,



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**TABLE 1** Next-Generation Sequencing With Distinct Gene Mutations (Black) in Urachal Carcinoma[a]

| Case No. | Type | Age, y | Stage | *TP53* | *KRAS* | *GNAS* | *SMAD4* | *KIT* | *PI3K3CA* | *NOTCH1* | *ATM* | *FGFR1* | *FGFR2* | *BRAF* | *KDR* | *PDGFRA* | *RB1* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | MU | 31 | IV | ■ | | | ■ | | | | | | | | | | |
| 2 | MU | 50 | III | | | | | | | | | | | | | ■ | |
| 3 | MU | 45 | III | ■ | ■ | ■ | | | | | | | | | | | |
| 4 | MU | 54 | IV | ■ | ■ | ■ | | | | | | | | | | | |
| 5 | MU | 62 | III | ■ | | | | | | | | | | | | | |
| 6 | MU | 46 | IV | ■ | ■ | ■ | | | | | | | | | | | |
| 7 | MU | 59 | III | ■ | | | ■ | ■ | | | | | | | | | |
| 8 | MU | 58 | IV | | | | ■ | | | | | | | | | | |
| 9 | MU | 50 | IV | ■ | ■ | ■ | | | | | ■ | | | | | | |
| 10 | MU | 52 | IV | | ■ | ■ | | | | | | | | | | | |
| 11 | MU | 56 | III | | | | | | | | | | | | | | |
| 12 | EN | 68 | IV | ■ | | | | ■ | | | | ■ | | | ■ | | |
| 13 | EN | 61 | IV | ■ | | | | | | | | | | | | | |
| 14 | EN | 47 | IV | ■ | ■ | | | | ■ | | | | ■ | | | | |
| 15 | EN | 69 | III | ■ | | | | | | ■ | | | | | | | |
| 16 | EN | 75 | IV | ■ | ■ | | | | | | | | | | | | |
| 17 | EN | 52 | IV | ■ | | | | ■ | | | | | | | | | |
| 18 | EN | 53 | III | ■ | | | ■ | | | | | | | | | | |
| 19 | EN | 59 | III | ■ | | | | | | | | | | | | | |
| 20 | EN | 51 | IV | ■ | | | | | | | | | | | | | |
| 21 | EN | 36 | III | ■ | | | ■ | | ■ | | | | | | | | |
| 22 | SR | 63 | III | ■ | | | ■ | | | | | | | | | | |
| 23 | SR | 71 | III | ■ | | | | | | | | | | | | | |
| 24 | SR | 66 | III | ■ | | | | | | | | | | | | | |
| 25 | SR | 50 | IV | | ■ | ■ | | | | | ■ | | | | | | |
| 26 | SR | 42 | IV | ■ | ■ | ■ | | | | | | | | | | | |
| 27 | SR | 33 | IV | ■ | | | ■ | | | | | | | | | | |
| 28 | SR | 52 | IV | ■ | | | | | ■ | | | | | | | | |
| 29 | SR | 67 | III | ■ | | ■ | | | | | | | | ■ | | | |
| 30 | NE | 24 | IV | ■ | | | | | | ■ | | | | | | | ■ |

EN, enteric subtype; MU, mucinous subtype; NE, high-grade neuroendocrine carcinoma subtype; SR, signet ring cell subtype.
[a]Stage was based on the Sheldon staging system.


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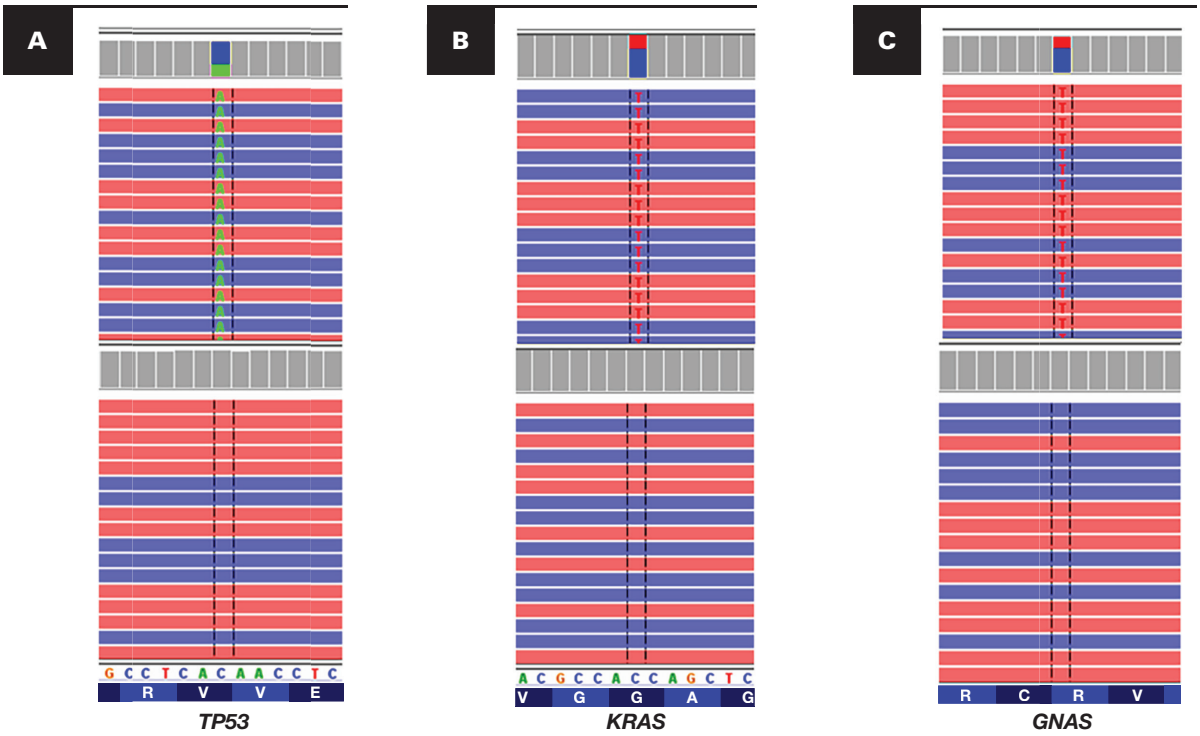


**FIGURE 2** Common genetic mutations (top) in urachal carcinomas vs normal (bottom). **A**, *TP53* gene mutation. **B**, *KRAS* gene mutation. **C**, *GNAS* gene mutation.

0.7-3.1 years). Patients with stage IV disease had a significantly lower survival rate than did those with stage III disease ($P = .005$). *KRAS* mutations were significantly more common in high-stage tumors ($P = .02$), as eight of the nine tumors with *KRAS* mutations were stage IV. *KRAS* mutations were also more frequent in younger patients ($P = .046$), as seven of the nine patients with *KRAS* mutations were younger than 53 years (the mean age of our cohort). Furthermore, *KRAS* mutations were associated with a significantly poorer overall survival ($P = .006$) in patients with urachal carcinoma FIGURE 3.

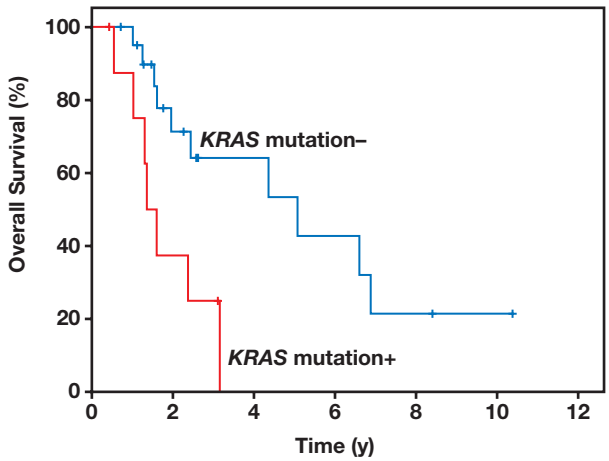


**FIGURE 3** Patients with *KRAS* mutations in urachal carcinoma showed a significantly poorer overall survival in the Kaplan-Meier curve ($P = .006$).

## DISCUSSION

There have been limited studies to investigate the molecular profile of urachal carcinoma, and most studies were conducted in a small series of cases due to the rarity of this malignant tumor.[10,12,18-24] Maurer et al[22] reported that urachal carcinoma expressed genomic alterations that were frequently present in bladder urothelial carcinoma and colorectal adenocarcinoma, suggesting that similar pathways might drive the tumorigenesis of these malignancies, despite the different tissue origins. However, Lee et al[23] found that urachal adenocarcinoma showed a distinct molecular signature from bladder urothelial carcinoma and colorectal adenocarcinoma, indicating that urachal carcinoma might use different oncogenic pathways from those in bladder and colorectal carcinomas. Recently, Reis et al[13] evaluated a large cohort of urachal carcinomas from multiple institutions, which demonstrated the prevalence of genetic mutations in urachal tumors. The most frequent mutations occurred in the *TP53* gene, followed by *KRAS*, *BRAF*, and *PIK3CA* genes. Furthermore, a considerable number of urachal carcinomas showed genomic aberrations in the RAS/RAF/PI3K signal transduction pathway, suggesting a potential value of anti–epidermal growth factor receptor therapy in this aggressive disease. However, only a small number of genes (12-15 genes) were analyzed by the targeted NGS test in this multi-institutional study.[13] In the current study, we conducted a mutational analysis of a cohort of urachal carcinomas from a single institution. Our NGS test included a large number of actionable or predictive genes (50-409), which demonstrated frequent mutations in *TP53*, *KRAS*, *GNAS*, and other genes.



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Importantly, our study reveals that several gene mutations are associated with distinct clinical and pathologic features in urachal carcinoma. *GNAS* mutations are present only in mucinous and signet ring cell subtypes, and *KRAS* mutations are more common in cancer stage IV and younger patients. Furthermore, the presence of the *KRAS* mutation in urachal carcinoma portends a significantly poorer overall survival. Nonetheless, due to the limited number of cases in our study, large independent cohort studies are needed to confirm the clinicopathologic significance of these gene mutations in urachal carcinoma.

Several studies have demonstrated that *TP53* is the most mutated gene in urachal carcinoma.[13,22-25] As a tumor suppressor, *TP53* inhibits cell cycle, particularly G1-S progression, and regulates DNA damage repair, cell proliferation, and apoptosis.[26] Mutations of the *TP53* gene have been reported in nearly half of all human malignancies, from a wide range of tumors, and are associated with poor prognosis and treatment failure in some cancers.[27] In the current study, our NGS analysis showed that the *TP53* gene was mutated in 75% of urachal carcinomas, particularly those with signet ring cell features; however, we did not observe any significant clinical association with the *TP53* gene mutations either. Reis et al[13] also found urachal carcinoma had frequent mutations in the *TP53* gene and expressed a high level of p53 protein, but neither *TP53* gene mutations nor p53 overexpression was associated with patient survival.[25] Nonetheless, targeted therapy against the *TP53* gene may still be useful in human cancers with *TP53* mutations, including urachal carcinoma.[28,29]

The *KRAS* gene is another frequently mutated gene in urachal carcinoma. This oncogene encodes a GTPase protein that plays a key role in the *RAS/MAPK* pathway.[30] When the *KRAS* gene is constitutively activated by gene mutation, it increases cell proliferation, inhibits apoptosis, and regulates tumor microenvironment and immune response.[30,31] Several studies have demonstrated that the *KRAS* mutation is often associated with a poor prognosis in adenocarcinomas of the lungs and gastrointestinal tract.[32,33] Sirintrapun et al[19] previously reported that the *KRAS* mutation was associated with a better overall survival in urachal carcinoma, but their cohort was small with only seven patients. In the current study, we studied a larger cohort of 30 patients and demonstrated that the *KRAS* mutation was significantly associated with high-stage disease and lower overall survival rate. The *KRAS* mutation also occurred more frequently in younger patients with urachal carcinoma in our cohort. Our findings are more in line with the previously known association between the *KRAS* mutation and poor prognosis at other anatomic sites.[32,33] In addition, two patients showed $KRAS^{G12C}$ mutants in our study, suggesting that $KRAS^{G12C}$ inhibitors might be useful in the targeted therapy for urachal carcinoma.[34]

A considerable number of urachal carcinomas exhibited genetic mutations in the *GNAS* gene in the current study. The *GNAS* gene encodes the guanine nucleotide binding protein (G protein) α stimulating activity polypeptide 1 and regulates the G protein function in signaling pathways.[35,36] Somatic mutations of *GNAS* have been found in several mucin-producing glandular neoplasms, such as intraductal papillary mucinous neoplasms of the pancreas and low-grade appendiceal mucinous neoplasms.[37,38] Nishikawa et al[37] reported that the *GNAS* mutation might regulate mucin production through the cyclic adenosine monophosphate–protein kinase A signaling pathway. Pietrantonio et al[39] found that the *GNAS* mutation may serve as a prognostic biomarker in patients with relapsed peritoneal pseudomyxoma receiving metronomic capecitabine and bevacizumab. In the current study, *GNAS* mutations were present only in mucinous and signet ring cell subtypes, reaffirming the regulatory role of GNAS in mucinous production, although *GNAS* mutations are not significantly associated with the clinical outcome.

Our study demonstrated that distinct gene mutations are associated with clinicopathologic features in urachal carcinoma, but there are several limitations in our study. First, we used different NGS platforms, which consisted of 50, 134, 146, or 409 gene targets. However, our analysis was focused on the initial 50 actionable or predictive gene markers, such as *TP53*, *KRAS*, and *GNAS*, that were covered in all the platforms. In addition, these expanded NGS platforms identified novel gene mutations in urachal carcinoma that have not previously been reported. Second, the number of patients was limited in our study, and most patients presented at an advanced stage (Sheldon stage III or IV) in this study, probably because of the tertiary referral nature of our institution. Our patients had an overall survival duration of 1.6 years, which was compatible with the results of previous studies.[1,6,8] Finally, our study was focused on pathologic features and clinical outcomes; the therapeutic implications of these gene mutations are beyond the realm of this study. Nonetheless, we identified a wide range of genetic mutations in urachal carcinoma, which may provide useful insight into potential therapeutic targets.

In conclusion, our NGS analysis of a large cohort of urachal carcinomas from a single institution demonstrates that gene mutations are highly frequent in this malignant disease. The most common mutations occur in the *TP53*, *KRAS*, and *GNAS* genes. Importantly, these gene mutations are associated with distinct clinicopathologic features. *GNAS* mutations are present only in urachal carcinomas with mucinous and signet ring cell features, and *KRAS* mutations are significantly associated with high-stage cancer and young patient age. Furthermore, the presence of the *KRAS* mutation portends a poor overall survival in patients with urachal carcinoma. Our results suggest that gene mutations may underlie the development of distinct clinicopathologic features in urachal carcinoma. Novel targeted therapies based on gene mutations may improve the treatment repertoire for this aggressive disease.

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