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Acquired Uniparental Disomy Regions Are Associated with Disease Outcome in Patients with Oral Cavity and Oropharynx But Not Larynx Cancers

Musaffe Tuna [1,*], Christopher I. Amos [1,2], Gordon B. Mills [3,4]

[1] Department of Medicine, Baylor College of Medicine, Houston, TX
[2] Institute of Clinical and Translational Research, Baylor College of Medicine, Houston, TX
[3] Department of Cell, Developmental & Cancer Biology, School of Medicine, Oregon Health Science University, Portland, OR
[4] Precision Oncology, Knight Cancer Institute, Oregon Health Science University, Portland, OR

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ABSTRACT

Acquired uniparental disomy (aUPD) regions pinpoint homozygousity and monoallelic expressed genes. We analyzed The Cancer Genome Atlas single-nucleotide polymorphism arrays and expression data from oral cavity, oropharynx, and larynx cancers to identify frequency of aUPD in each tumor type and association of aUPD regions and differentially expressed genes in the regions with survival. Cox proportional hazard models were used for survival function; and Student's *t* test, for differentially expressed genes between groups. The frequency of aUPD was highest in larynx cancers (88.35%) followed by oral cavity (81.11%) and oropharynx cancers (73.85%). In univariate analysis, 11 regions at chromosome 9p were associated with overall survival (OS) in oral cavity cancers. Two regions at chromosome 17p were associated with OS in oropharyngeal cancers, but no aUPD region was associated with survival in patients with larynx cancers. Overexpression of SIGMAR1, C9orf23, and HINT2 was associated with reduced OS in patients with oral cavity cancers, and upregulation of MED27 and YWHAE was associated with shorter OS in patients with oropharynx cancers. In multivariate analysis, four aUPD regions at chromosome 9p and overexpression of HINT2 were associated with shorter OS in oral cavity cancers, and overexpression of MED27 was associated with worse OS in patients with oropharynx cancers. aUPD regions and differentially expressed genes in those regions influence the outcome and may play a role in aggressiveness in oral cavity and oropharynx cancers but not in patients with larynx cancers.
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Introduction

Head and neck squamous cell carcinoma (HNSCC) is a heterogeneous disease that presents in multiple sites of head and neck; oral cavity, oropharyngeal, larynx, and hypopharynx [1]. The incidence of new cases with oral cavity, oropharyngeal, larynx, and hypopharyngeal cancers is increasing especially among young people worldwide, with an estimated 760,000 incident cases and 380,000 deaths during 2018 [2,3]. DNA copy number alterations, LOH, genetic mutation, mRNA and miRNA expression, and their association with outcome are well characterized in subtypes of HNSCCs [1,4–10]. However, the frequency and distribution of acquired uniparental disomy (aUPD) in patients with oral cavity, oropharynx and larynx cancers, and its association with outcome of disease have not been deeply explored. aUPD studies in HNSCCs are limited [11,12], with no reports presenting associations between aUPD regions and subtypes of HNSCCs. As a concept, aUPD, which constitutes either segmental or whole chromosome homozygousity with monoallelic expressed genes, was first introduced by Engel in 1980 [13]. Segmental aUPD arises through mitotic recombination [14], while whole chromosome aUPD occurs by deletion of one chromosome and reduplication of the remaining allele [13]. Breakage-fusion-bridge cycles may provide another mechanism that can lead to aUPD [15]. Previously, we showed the association between aUPD regions and epidemiologic factors in subtypes of HNSCCs [16]. The current study is conceived to address the frequency and distribution of aUPD regions in each organ side. We further tested association of aUPD regions with disease outcome and differentially expressed genes between samples with and without aUPD in patients with oral cavity, oropharynx, and larynx cancers.

Materials and Methods

The Cancer Genome Atlas (TCGA)–generated HNSCCs data were analyzed in this study. We obtained genotyping data from the GDC website (https://portal.gdc.cancer.gov). Expression and clinical data were acquired from the XENA website (https://xenabrowser.net). HNSCCs are a heterogeneous group of cancers that include oral cavity, oropharyngeal, larynx, and

* Address all correspondence to: Musaffe Tuna, Department of Medicine, Baylor College of Medicine, Houston, TX.
E-mail address: mtuna9@gmail.com. (M. Tuna).

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hypopharynx cancers. Cancers in the buccal mucosa, floor of mouth, hard palate, lip, oral cavity, oral tongue, and alveolar ridge are considered oral cavity cancers [1]. Cancers in the tonsil, soft palate, base of tongue, and oropharynx are considered oropharyngeal. Patient characteristics are summarized in Supplementary Table S1.

Genomic Analysis

Genotyping Console software (Affymetrix) was used to generate CHP files and to perform QC. A total of 448 samples (448 tumor and 448 matching normal, in total 896 samples) passed QC, and 270 of these tumors were oral cavity, 65 tumors were oropharynx, 103 tumors were larynx, and 10 tumors were hypopharynx cancers. Copy Number Analyser for GeneChip v4.0 (http://www.genome.umin.jp) was used to analyze aUPD regions by using tumor and matching normal samples data as described earlier [17]. The smallest overlapping regions of aUPD were determined by comparing aUPD endpoints (3′ and 5′). Gene localization was determined by using NCBI Build GRCh38/38 genome browser (http://genome.ucsc.edu).

Statistical Analysis

Disease outcome end points in survival analysis were overall survival (OS) and recurrence-free survival (RFS). OS was considered from date of diagnosis until date of death or last follow-up, while RFS was calculated to date of detection of progression or death, or last follow up. Recurrence was defined as evidence of local recurrence, new lymph node, or distant metastasis. High and low level expression of genes was determined by using median as cutoff point. Univariate Cox proportional hazard model was used for survival analysis. Kaplan-Meier plot was used to estimate survival probabilities, and log-rank test was used to compare them. Multivariate Cox proportional hazard model was used to determine prognostic markers. All covariates were included in multivariate analysis. This study adheres to REMARK criteria [18]. The Student's two-tailed t test was used to compare expression of genes between groups. We evaluated the P values by applying the Benjamini-Hochberg false discovery rate (FDR) [19]. STATA v10 (STATA Corp., College Station, TX) was used to perform the statistical analyses.

Results

Frequency of aUPD Correlates with Oral Cavity and Larynx Cancer Clinical Features

We analyzed TCGA generated Affymetrix genotyping arrays data from 270 oral cavity, 103 larynx, 65 oropharynx, and 10 hypopharynx cancers. The frequency of aUPD is significantly different among organ sites (P = .0021). Any aUPD was most common in patients diagnosed with larynx cancer (88.35%) (range 0-14; median, 4; mean, 4.55), followed by oral cavity (81.11%) (range, 0-16; median, 3; mean, 3.17) and hypopharynx (75.0%) (range, 0-27; median, 2.5; mean, 8). The prevalence of aUPD was lowest in cases diagnosed with oropharynx (73.85%) (range, 0-13; median, 2; mean, 2.88). The most frequent aUPD was at chromosome 9p (34.44%), 9q (28.89%), and 17p (28.89%) in oral cavity; at chromosome 17p (45.63%), 9q (31.07%), and 9p (29.13%) in patients with larynx cancers; at chromosomes 9q (20.0%), and 17p (16.92%) in oropharynx; and at chromosomes 9q (50%), 17q (50%), and 17p (37.5%) in hypopharynx. Due to the small sample size, we excluded hypopharynx samples from further analysis.

aUPD Regions Are Associated with Survival

We identified 17 small overlapping regions (SORs) including the CDKN2A region among the most frequent aUPD regions at chromosome 9p (11 regions), 9q (4 regions), and 17p (2 regions). Next, we tested whether any of these SORs were associated with survival in oral cavity, oropharynx, and larynx HNSCC. When we randomly divided samples into training and test sets, nine regions at chromosome 9p (9p24.3, P = .046; 9p24.1, P = .046; 9p23-p22.3, P = .029; 9p22.3-p22.2, P = .029; 9p21.3_1, P = .008; 9p21.3_2, P = .018; 9p21.3-p21.2, P = .018; 9p21.2, P = .027; and 9p13.3, P = .041, respectively) were associated with shorter OS in training, and of these, eight regions at chromosome 9p (9p24.3, P = .034; 9p24.1, P = .018; 9p23-p22.3, P = .011; 9p22.3-p22.2, P = .017; 9p21.3, P = .039; 9p21.3_1, P = .040; 9p21.3_2, P = .029; 9p21.2, P = .040, respectively) remained associated with poor OS in the test set (Supplementary Table S2). However, none of regions remained significant after multiple correction test in training and test sets. This could be due to small sample size. Thus, to increase the statistical power, we performed univariate analysis in all samples with oral cavity cancers. In univariate Cox regression analysis for OS, all regions at chromosome 9p (9p24.3, P = .004; 9p24.1, P = .002; 9p23-p22.3, P = .001; 9p22.3-p22.2, P = .001; CDKN2A, P = .008; 9p21.3_1, P = .002; 9p21.3_2, P = .003; 9p21.3-p21.2, P = .012; 9p21.2, P = .004; 9p21.1, P = .025; and 9p13.3, P = .032) were associated with poor OS in patients with all oral cavity tumors regardless of HPV status (Figure 1, Supplementary Table S2). No association was found between aUPD regions and RFS time in all samples with oral cavity cancers (Supplementary Table S2). In multivariate analysis corrected for the base model including all covariates, aUPD regions at chromosome 9p24.1 (P = .041, q = 0.049), 9p21.2 (P < .0001, q < 0.0001), 9p21.1 (P = .020, q = 0.033), and CDKN2A (P = .049, q = 0.049) were significantly associated with OS in all samples with oral cavity cancers (Table 1).

However, in patients with oropharyngeal cancers, in univariate analysis, two regions at chromosome 9q (9q31.3, P = .033 and 9q34.13, P = .033) and two regions at chromosome 17p (17p13.3, P < .0001 and 17p12, P = .002) were associated with worse OS (Figure 2, Supplementary Table S3). In multiple testing (Benjamini-Hochberg FDR), only aUPD region at chromosome 17p13.3 (q < 0.0001) remained associated with poor OS in oropharyngeal cancers. No association was found between aUPD regions and RFS in patients with oropharyngeal cancers (Supplementary Table S3). aUPD region at chromosome 17p13.3 remained predictor of OS (P < .0001, q < 0.0001).The sample size was too small to divide into training and test tests.

Of note, in univariate analysis, none of aUPD regions were associated with OS and RFS time in patients with larynx cancers. However, age under 50 (P = .009, q = 0.090) and being female (P = .003, q = 0.060) were associated with shorter OS time, and only age (P = .001, q = 0.019) was significantly associated with RFS time in all samples with larynx cancers (Supplementary Table S4). No association was found in the training set. In multivariate analysis, no predictor was found for OS and RFS in patients with larynx cancers.

Differentially Expressed Genes in aUPD Regions Are Associated with Survival

We analyzed all 78 ORFs in the 11 SOR aUPD regions that were associated with OS in oral cavity tumors to identify differentially expressed genes between samples with and without aUPD regions at the same locus (Supplementary Table S5). Twenty-six out 78 genes were differentially expressed in patients with oral cavity tumors. Only 2 out of 26 genes had lower expression, and the remaining 24 genes had higher expression in samples with aUPD compared to samples without aUPD (Supplemental Table S5). Next, we determined whether any of the differentially expressed genes had an impact on survival time. In univariate analysis, expression of only three genes at chromosome 9p, HINT2 (P = .007, q = 0.021), SIGMAR1 (P = .035, q = 0.045), and C9orf23 (P = .045, q = 0.045), was associated with poor OS in all patients with oral cavity cancers (Figure 3). Expression of only one gene, NUDT2 (P = .023), was associated with shorter RFS in all patients with oral cavity cancers. All four genes (9p13.3) had higher expression in samples with aUPD compared to samples without aUPD in the same locus. In multivariate analysis, expression of HINT2 (P = .037) remained as an independent predictor of OS in all samples with oral cavity cancers. We then compared expression of SIGMAR1, C9orf23, and HINT2 in oral

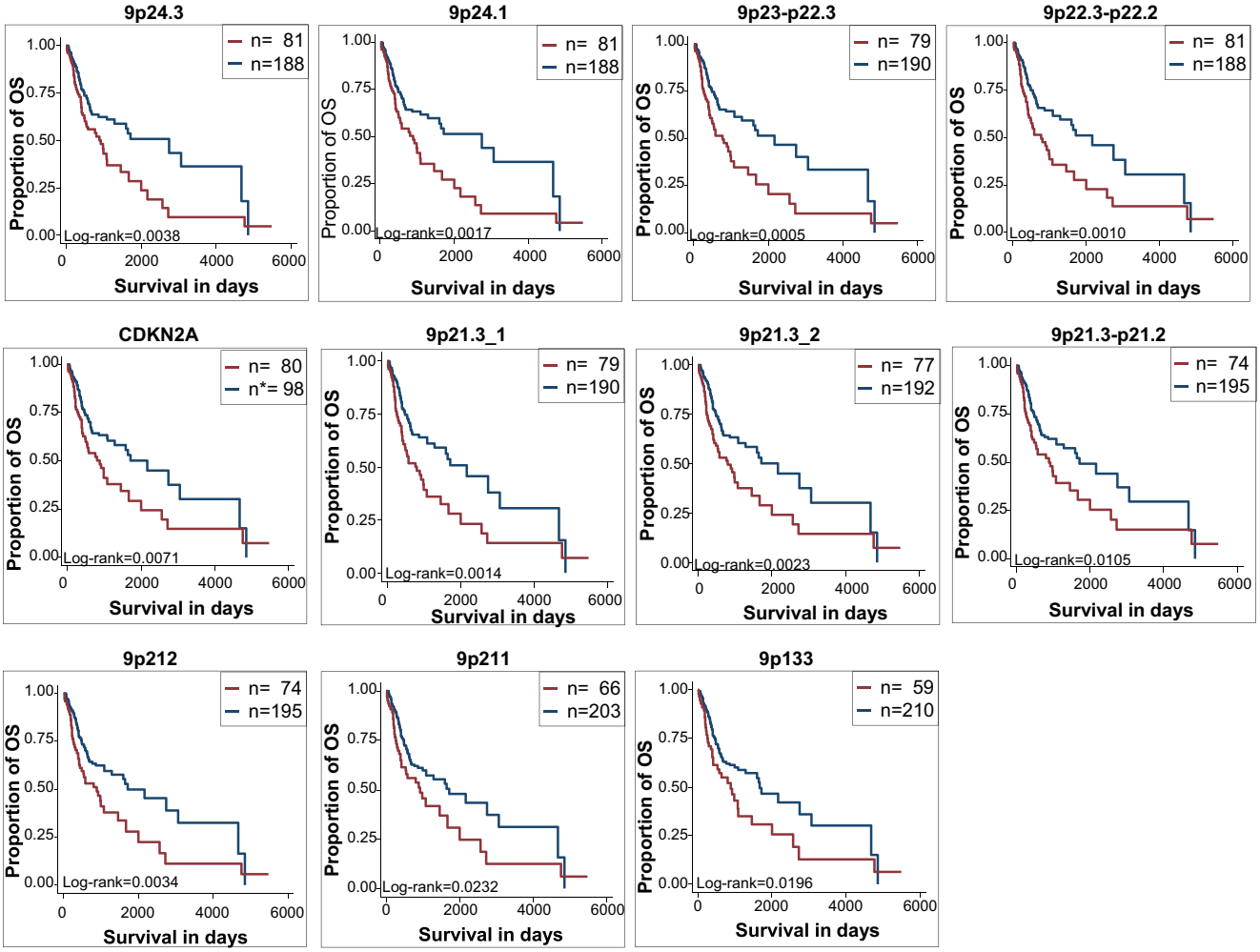

Figure 1. Kaplan-Meier plots of overall survival for aUPD at chromosomes 9p in all patients with oral cavity cancers.

cancer tissues with matching normal oral tissues which are UPD positive for the relevant region. SIGMAR1 expression is significantly higher in oral cavity tumor tissues compared to matching normal tissues (P = 7.49E-05, q = 2.25E-04), while expression of C9orf23 (P = .593, q = 0.593) and HINT2 (P = .384, q = 0.575) is not statistically significant between tumor and normal tissues. However, we have not ruled out the possibility that these genes might also be overexpressed in adjacent normal tissue. No association was found between expression of genes and smoking status, alcohol intake, and HPV status in oral cavity cancers.

For oropharynx cancer, we analyzed all 20 genes in the 4 SOR aUPD regions that were associated with OS to identify differentially expressed genes. Four genes had significantly higher expression in samples with aUPD compared to samples without aUPD at the 9q and 17p respective loci. In univariate analysis, only two genes, MED27 (P = .002, q = 0.002) and YWHAE (P = .002, q = 0.002) (Figure 3), were significantly associated with shorter OS but were not associated with RFS. In multivariate analysis, expression of MED27 (P = .036) remained a predictor for worse OS in oropharyngeal cancers. In oropharyngeal cancer, the TCGA data do not have enough matching normal samples. Thus, we compared expression of MED27 and YWHAE between UPD-positive oropharyngeal cancer samples to normal oral cavity samples. Expression of MED27 (P = 2.27E-05, q = 5.675E-05) is significantly higher in oropharyngeal cancer samples compared to normal tissues, while expression of YWHAE does not significantly differ. We found a significant association between overexpression of MED27 (P = .020) and YWHAE (P = .020) and smoking in oropharynx cancers, while no association was found with alcohol intake.

Discussion

In this study, we identified aUPD regions that were associated with survival, specific for oral cavity and larynx cancers. In univariate analysis, 11 aUPD regions at chromosome 9p were associated with poor OS. In multivariate analysis, only four aUPD regions at chromosome 9p were significantly associated with poor OS. In contrast, none of the SORs at 9p were associated with OS and/or RFS in patients with oropharyngeal cancers. However, aUPD regions at chromosomes 9q31.3, 9q34.13, 17p13.3, and 17p12 were associated with shorter OS in oropharyngeal cancers. These data indicated that differentially expressed genes in aUPD regions at chromosome 9p are likely to contribute to oral cavity cancer pathophysiology and that differentially expressed genes in aUPD regions at chromosome 9q and 17p may play important role in tumorigenesis of oropharynx cancers. Among the 26 differentially expressed genes between samples with and without aUPD, only 3 genes that were differentially expressed (C9orf23, SIGMAR1 and HINT2) were associated with OS in oral cavity cancers. SIGMAR1 (sigma nonopioid intracellular receptor 1) encodes stress activated chaperon protein (Sigma1, also known as aging-associated gene 8) that communicates between the endoplasmic reticulum and mitochondrion and plays a crucial role in ion homeostasis. Expression of Sigmar1 regulates cell survival through controlling calcium homeostasis [20] and modulates invasiveness and angiogenesis in glioblastoma cell lines via human voltage-dependent K+ channel human ether-a-go-go–related gene (hERG) and subsequent formation of hERG/β-integrin signaling complex and consequently activation of the PI3K/AKT pathway, and

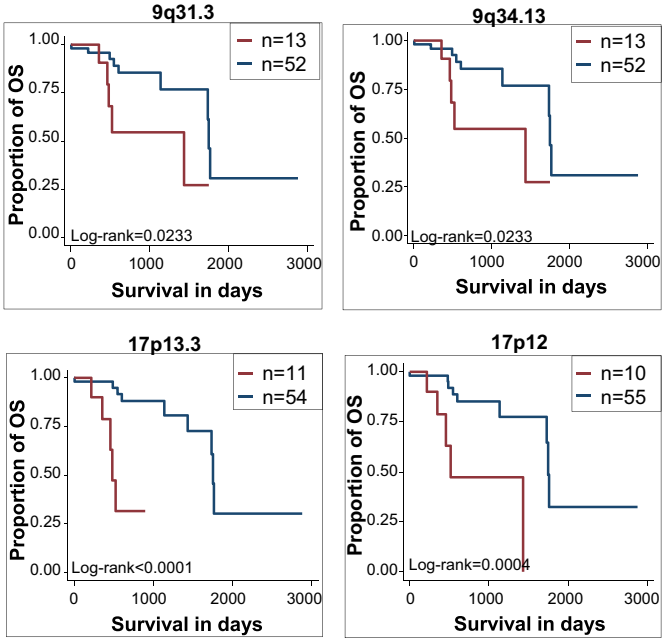

Figure 2. Kaplan-Meier plots of overall survival for aUPD at chromosomes 9q and 17p in oropharyngeal cancers.

VEGF expression in myeloid leukemia and colorectal cancer cells [21–23]. Moreover, SIGMAR1 overexpression is associated with poor survival in myeloid leukemia and colorectal cancer [22]. hERG1 is also overexpressed in colorectal cancers [24] and is an independent prognostic factor for worse outcome in early stage colorectal cancer [25]. Sigmar1 also interacts with CI channels to regulate the cancer cell cycle [26]. Moreover, blocking Sigma1 in Sigma1-expressing triple-negative breast and androgen-independent prostate cancer cells by Sigma1 inhibitor and RNAi, lead to suppression of PD-L1 expression and functional interaction of PD-1 and PD-L1 in cancer cells and co-cultured T-cells [27]. Taken together, expression of SIGMAR1 may play an important role in oral tumorigenesis and progression, and these data collectively pinpoint Sigma1 as a potential target for oral cavity cancer therapy. Further studies are needed to determine function of this gene in oral cavity cancers. NUDT2 encodes a member of the MutT family of nucleotide pyrophosphatases, overexpresses in breast cancers, and promotes cell proliferation in breast cell lines [28]. HINT2 (histidine triad nucleotide binding protein 2) encodes nucleotide hydrolases and transferases, and localizes in mitochondria. Hint2 modulates Ca^{2+} pumping into mitochondria [29]. Biologic function of overexpression of HINT2 and C9orf23 in cancers is unknown.

In oropharynx cancer, only four genes in the aUPD regions were differentially expressed between samples with and without aUPD. However, only

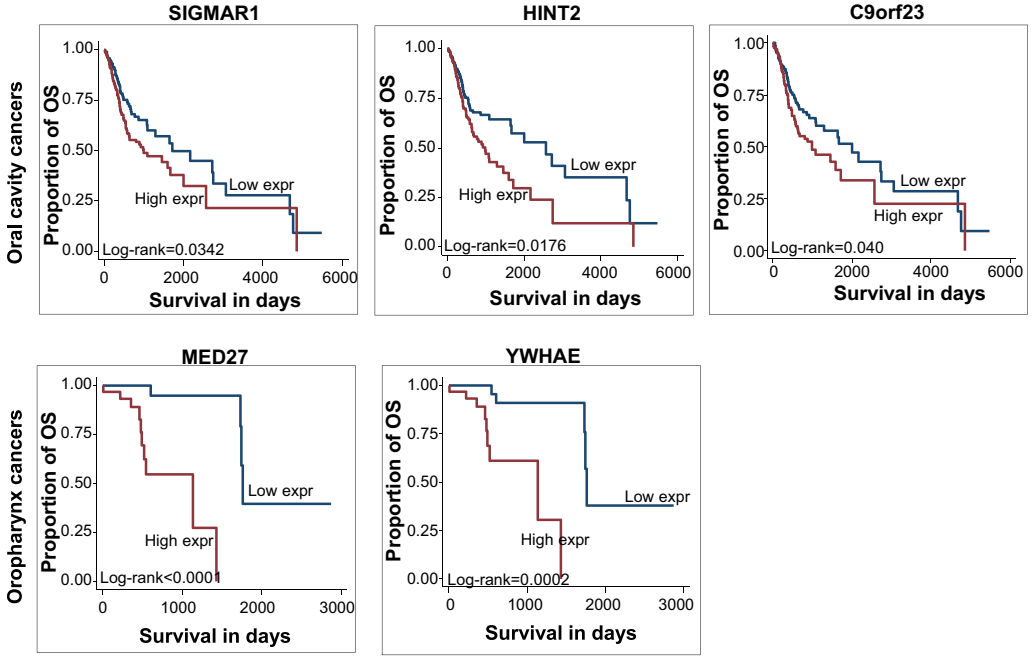

Figure 3. Kaplan-Meier plots of overall survival for differentially expressed genes between samples with and without aUPD in all patients with oral cavity (SIGMAR1, HINT2, and C9orf23) and oropharynx (MED27 and YWHAE) cancers. The median gene expression levels was used as cut points to classify tumors as high and low.

Table 1
Multivariate Analysis of Genetic Covariates for OS in All Patients with Oral Caviy Cancers

Covariates	HR	95%CI	*P*	*q*
aUPD regions				
9p24.1	0.04	0.002-0.88	.041	0.049
9p21.2	1.16E + 09	5.40E + 07-2.48E + 10	< .0001	< 0.0001
9p21.1	0.21	0.07-0.78	.020	0.033
CDKN2A	0.16	0.03-0.99	.049	0.049

HR, hazard ratio; *CI*, confidence interval; *q*, Benjamini-Hochberg FDR. All covariates are included in multivariable analysis.

MED27 (mediator complex subunit 27) and YWHAE (tyrosine 3/tryptophan 5-monooxygenase activation protein epsilon) were associated with shorter OS. MED27 (mediator complex subunit 27) encodes a component that subunit of a multiple protein complex involved in the regulation of activator-dependent transcription. Overexpression of MED27 plays role in cell proliferation, invasion, and metastasis through Wnt/b-catenin pathway *in vivo* and *in vitro* in adrenal cortical carcinogenesis, and silencing MED27 inhibits adrenal cortical carcinogenesis and epithelial-mesenchymal transition [30]. Its expression contributes to cell growth by activating AKT/MAPK and NF-kB/iNOS pathways in melanoma [31]. Moreover, miR-18a inhibits cell growth and induces apoptosis by downregulating the MED27 and Akt phosphorylation in osteosarcoma [32]. The YWHAE (also known as 14-3-3e) belong to the 14-3-3 family of proteins. It interacts with CDC25, RAF1, and IRS1 proteins, indicating diverse roles in cellular function including cell proliferation [33–35]. Overexpression of YWHAE (14-3-3ε) promotes epithelial-mesenchymal transition and cell migration [36], and predicts tumor metastasis and poor survival in hepatocellular carcinoma [37]. Moreover, overexpression of YWHAE advances cell proliferation, metastasis, and chemoresistance in breast cancer cells [38]. Upregulated expression of cytoplasmic 14-3-3β, γ, ε, ζ, η, and τ is associated with advanced disease and aggressive features. The β and ε isoforms are independent poor prognostic factors in vulvar squamous cell carcinoma [39], and overexpression of YWHAE is a predictor for poor OS and chemotherapy resistance in patients with advanced extra nodal natural killer/T-cell lymphoma [40].

Over expression of SIGMAR1, C9orf23, HINT2, and NUDT2 may contribute to the behavior of oral cavity cancers, whereas upregulation of MED27 and YWHAE may contribute to tumorigenesis of oropharynx cancers. Further functional studies are warranted to identify the roles of these genes in progression or therapy resistance in oral cavity and oropharynx cancers.

In larynx cancers, patients with age of onset under 50 have shorter OS and RFS than those patients having age over 50. This could be because patients under 50 years of age are more likely to have a higher grade and later stage: 9 of 11 samples were stage 4, 1 was stage 3, and 1 was stage 2. Moreover, women were found to have a shorter OS than men. This could be because of the 70.59% of women were current smokers and 29.41% were former smokers, while 41.13% of men were current smokers and 44.83% were former smokers in this cohort. Although larynx cancers are more frequent in men than women, these cancers may be more aggressive in women.

In summary, we identified different aUPD regions that are associated with shorter OS in oral cavity and oropharynx cancers but not in larynx cancers. Differentially expressed genes between samples with aUPD and without aUPD in the same regions were also associated with survival. These differentially expressed genes may play a role in aggressiveness of oral cavity and oropharyngeal cancers.

Conflict of Interest

The authors declare that they have no conflict of interest. The authors declare that they have no competing interests with this study. G. B. M. receives support or acts as a consultant for: AstraZeneca, ImmunoMET, Ionis, Nanostring, PDX Pharmaceuticals, Signalchem Lifesciences, Symphogen, and Tarveda.

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