Comprehensive genomic profiles of metastatic and relapsed salivary gland carcinomas are associated with tumor type and reveal new routes to targeted therapies

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Background: Relapsed/metastatic salivary gland carcinomas (SGCs) have a wide diversity of histologic subtypes associated with variable clinical aggressiveness and response to local and systemic therapies. We queried whether comprehensive genomic profiling could define the tumor subtypes and uncover clinically relevant genomic alterations, revealing new routes to targeted therapies for patients with relapsed and metastatic disease.

Patients and methods: From a series of 85,686 clinical cases, DNA was extracted from 40 µm of formalin-fixed paraffin embedded (FFPE) sections for 623 consecutive SGC. CGP was carried out on hybridization-captured, adaptor ligation-based libraries (mean coverage depth, >500×) for up to 315 cancer-related genes. Tumor mutational burden was determined on 1.1 Mb of sequenced DNA. All classes of alterations, base substitutions, short insertions/deletions, copy number changes, and rearrangements/fusions were determined simultaneously.

Results: The clinically more indolent SGC including adenoid cystic carcinoma, acinic cell carcinoma, polymorphous low-grade adenocarcinoma, mammary analog secretory carcinoma, and epithelial–myoepithelial carcinomas have significantly fewer genomic alterations, TP53 mutations, and lower tumor mutational burden than the typically more aggressive SGCs including mucoepidermoid carcinoma, salivary duct carcinoma, adenocarcinoma, not otherwise specified, carcinoma NOS, and carcinoma ex pleomorphic adenoma. The more aggressive SGCs are commonly driven by ERBB2 PI3K pathway genomic alterations. Additional targetable GAs are frequently seen.

Conclusions: Genomic profiling of SGCs demonstrates important differences between traditionally indolent and aggressive cancers. These differences may provide therapeutic options in the future.

Key words: salivary gland cancer, head and neck cancer, genomic alteration, PI3K, TP53, ERBB2

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Introduction

Salivary gland carcinomas (SGCs) are rare histologically diverse malignancies whose prognosis varies from indolent to aggressive depending upon histology, grade, and stage [1]. Examples of SGCs include those that tend to have more indolent clinical courses, such as adenoid cystic carcinomas (ACC), acinic cell carcinoma (AciciC), polymorphous low-grade adenocarcinoma (PLGA), mammary analog secretory carcinoma (MASC), and myoepithelial carcinoma (myoepi). Tumors with generally worse prognosis such as mucoepidermoid carcinoma (MEC), salivary duct carcinoma (SDC), adenocarcinomas not otherwise specified (AD-NOS), carcinomas not otherwise specified (CA-NOS), and carcinoma ex pleomorphic adenosin (ca ex PA) [2, 3] though there is still variation of behavior within each histologic subtype. The standard curative therapy is surgery followed by radiation, but the role of chemotherapy with radiation is controversial and treatments in the relapsed/metastatic setting are often inadequate [4, 5].

Studies using next-generation sequencing (NGS) techniques focusing on specific histologies, such as SDC, MEC, and ACC, have started to identify key molecular pathways in SGCs such as HER2 (ERBB2) and PI3K. Limited studies have evaluated multiple histologies simultaneously but have been hampered by small sample size [6, 7]. Additionally, there are scant data on tumor mutation burden (TMB) in SGCs, a potentially critical element for response to immunotherapy [8]. In the following study, we present novel and expanded comprehensive genomic profiling (CGP) of a large series of SGCs, additional data on TMB for previously presented cases, and comparisons between SGC histologic subtypes.

Methods

Full methods can be found in the supplementary Methods, available at Annals of Oncology online, and have been described previously [9]. Briefly, from a series of 85 686 clinical cases, a series of 623 clinical cases of SGC were analyzed using CGP in a Clinical Laboratory Improvement Amendments (CLIA)-certified, CAP (College of American Pathologists)-accredited laboratory (Foundation Medicine, Cambridge, MA). Approval for this study, including a waiver of informed consent and a HIPAA waiver of authorization, was obtained from the Western Institutional Review Board. The pathologic diagnosis of each case was confirmed on routine hematoxylin and eosin (H&E) stained slides and all samples forwarded for DNA extraction contained a minimum of 20% tumor nuclear area, compared with benign nuclear area. GCP was carried out as described previously [10]. TMB was determined on 1.1 megabases (Mb) of sequenced DNA for each case based on the number of somatic base substitution or indel alterations per Mb after filtering to remove known somatic and deleterious mutations [8].

Results

Sequencing results for 623 SGCs by histologic subtype are summarized in Table 1 and Figure 1. The tumors segregated into groups based upon TP53 status and TMB. Histologies tending to be lower grade and more clinically indolent, including ACC, AciciC, PLGA, myoepi, and MASC had fewer median GAs/tumor (2.1) than more aggressive tumors (4.3) (P < 0.001). Moreover, more indolent SGCs harbored TP53 GAs <20% of the time compared with typically more aggressive, higher grade tumors having TP53 mutations rates of >40% (P < 0.001) (Table 1). Interestingly, tumor classification by TP53 status correlated with TMB. Histologies harboring <20% TP53 GAs all had TMB >10 mut/Mb rates of ≤5%, whereas tumors with TP53 mutation rates >40% had TMB >10 mut/Mb rates of >10% (P < 0.001 between indolent and aggressive tumors). Within histologic subtypes TMB was assessed by grade. For ACC and MEC, the TMB remained low in both low-grade and high-grade cases. For the ducal adenocarcinoma and adenocarcinoma NOS categories, the TMB was higher in the high-grade tumors than in the low-grade tumors, but this difference did not reach statistical significance. These data suggest the clinical aggressiveness of different SGC histotypes may be related, in part, to the degree of TP53 mutations and TMB.

ERBB2 and PIK3CA GAs were noteworthy in several tumors. There were ERBB2 GAs, typically amplifications, observed in at least 13% of all the higher grade tumors with SDC having ERBB2 GAs in 32%. In fact, the ERBB2 GA frequency in SDCs was the highest of the 400 histologic cancer subtypes sequenced within the 85 686 case Foundation Medicine cohort. None of the more clinically indolent tumors had ERBB2 GAs (P < 0.001 between more indolent and aggressive tumors). TP53 mutations were seen in 87% of ERBB2 amplified tumors. The frequency of PIK3CA GAs was also elevated in most of the more aggressive histologies, occurring in ≥20% of MEC, SDC, AD-NOS, and CA-NOS. Unlike ERBB2, however, PIK3CA GAs were also seen in more indolent tumors, though less frequently (P < 0.001). BRAF GAs were seen infrequently (0%–5% per histotype, 2.7% overall). Most BRAF GAs were short variants (SV; 46% of which were V600E and 33% were activating non-V600E base substitutions) and 12% were fusions retaining the kinase domain. The TP53 co-GA frequency in the BRAF mutated SGC was 41%.

In addition to the aforementioned GAs, each lower grade histologic subtype had a unique GA profile. ACC: There was a mean frequency 1.6 total GA/tumor, with the characteristic MYB-NFIB gene fusion identified in 23% of cases (Table 1; Figure 1A). Overall, the frequency of potentially targetable GAs, including PDGFRα and KIT, was low with no major genomic target present in greater than 5% of cases. AciciC: There was a mean frequency of 2.8 GA/tumor (Table 1; Figure 1B). Noteworthy additional alterations were in PTEN (9%), FBXW7 (8%), ATM (7%), and NFI (5%). PLGA: There were 1.6 GA/tumor with only a single potentially targetable GA in PTEN (Table 1; Figure 1C). Myoepithelial: The median GA/tumor was 3.0. BRAF GA frequency was 5% and there were limited GAs in the PI3K/MTOR pathway (PIK3CA mutation and RICTOR amplification), the sonic hedgehog pathway (PTCH1) and rare kinase growth factor GA (PDGFR) (Table 1; Figure 1D). MASC: There was a mean of 2.8 GA/tumor and all 12 (100%) of the cases featured the signature t(12;15) (q13;q25) ETV6-NTRK3 gene fusion (Table 1; Figure 1E). More frequently mutated SGCs also harbored unique GA profiles. MEC: The median was 4.2 GA/tumor and BRAF alterations were discovered in 4% (Table 1; Figure 1F). Other clinically relevant GAs included FGFR1, BRCA2, and PTEN each altered in 8% of cases. SDC: There was a median 3.6 GA/tumor. Slightly >2% of SDC featured an activating ERBB2 SV GA only and lacked evidence of ERBB2 amplification (Table 1; Figure 1G). There were also multiple additional clinically relevant GA involving PTEN.
Table 1. Clinical characteristics and genomic alterations in 10 different salivary gland cancer histologic subtypes

|                          | Typically low-grade salivary gland cancers (n = 264) | Typically higher grade salivary gland cancers (n = 359) |
|--------------------------|-----------------------------------------------------|-------------------------------------------------------|
|                          | Adenoid cystic carcinoma | Acinic cell carcinoma | Polymorphous low grade adenocarcinoma | Myo-epithelial carcinoma | Mammary analog secretory carcinoma | Muco-epidermoid carcinoma | Salivary duct carcinoma | Adenocarcinoma, not otherwise specified | Carcinoma, not otherwise specified | Carcinoma ex pleomorphic adenoma |
| Patients (N)             | 154 | 73 | 5 | 20 | 12 | 57 | 44 | 117 | 119 | 22 |
| GAs/tumor                | 1.6 | 2.8 | 1.6 | 3.6 | 2.8 | 62 | 3.6 | 4.1 | 61 | 2 |
| Median age in years      | 55  | 55 | 72 | 56 | 62 | 42 | 58 | 67 | 63 | 62 |
| Gender (% female/% male) | 50% F | 54% F | 80% F | 42% F | 38% F | 62% M | 46% F | 18% F | 26% F | 35% F | 50% F |
| Significant GAs (%)      | MYB-NFIB (65) | PTEN (10) | TSC2 (20) | PIK3CA (15) | RICTOR (15) | ETV6-NTRK3 (100) | PIK3CA (20) | ERBB2 (13) | PIK3CA (27) | PIK3CA (20) | FGFR1-PLAG (9) |
| TP53 GA frequency (%)    | 4  | 10 | 0 | 13 | 17 | 43 | 67 | 55 | 48 | 46 |
| ERBB2 GA frequency (%)   | 0  | 0 | 0 | 0 | 0 | 13 | 32 | 17 | 15 | 2 |
| PIK3CA GA frequency (%)  | 5  | 3 | 0 | 15 | 0 | 20 | 27 | 24 | 20 | 0 |
| BRAF GA frequency (%)    | 0  | 3 | 0 | 5 | 0 | 4 | 5 | 4 | 4 | 0 |
| Tumor mutational burden  | 1  | 3 | 0 | 5 | 0 | 10 | 14 | 10 | 2 | 12 |
| Potential for targeted therapies | Low | Limited | Moderate | High | High | Moderate | High | Moderate | Moderate | High |

GA, Genomic alterations.
Figure 1. Long tail genomic analysis of the 50 most frequently altered genes in the 10 sub-types of relapsed and metastatic salivary gland cancers. NOS, not otherwise specified.
(17%), RICTOR and CDK4 (7%), FGFR1 and BRAF (5%), and RET (2%). Interestingly, only one ERBB2 amplified SDC harbored a PIK3CA mutation (Table 1; Figure 1H). AD-NOS: The median GA/tumor was 4.1. Interesting GAs included EGFR (5%) (Table 1; Figure 1H). CA-NOS: This group included SGCs that could not be further subdivided based upon the submitted specimen, and had a median GA/tumor of 5.2 (Table 1; Figure 1I). Potentially targetable GA included PTEN and NF1 involving the MTOR pathway, each identified in 8% of the CA-NOS group. At 21%, the CA-NOS patients had the highest frequency of TMB > 10 mut/Mb of all the mSG subtypes. Ca ex PA: There was a median 3.0 GA/tumor (Table 1; Figure 1I). Noteworthy GAs included alterations of PTEN (14%) and FGFR1 and FGFR2 (9%). One FGFR1 amplification co-occurred with ERBB2 amplification and the second FGFR1 GA was an FGFR1-PLAG fusion, which is likely not activating.

Despite their relative rarity, there was evidence of targeted therapy usage based upon NGS results, often with clinical benefit. Examples are given in Table 2. One newly reported case is a 63-year-old man with a MASC harboring an ETV-NTRK3 translocation. Before the development of NTRK3 inhibitors, he was placed on study combining an oral PIK3 inhibitor and an oral EGFR tyrosine kinase inhibitor. The patient had a minor response to therapy (Figure 2) and was on therapy for 2.5 years after having rapid progression before starting therapy. Unfortunately, targeted therapy does not always work, as demonstrated by a patient with an AciCC harboring an activating BRCA2 GA who did not respond to olaparib, a PARP inhibitor.

**Discussion**

In this study of >600 SGCs, we identified mutation patterns between less and more aggressive histotypes, provided novel NGS data for AciCCs, PLGAs, myoepi, and MASC, expanded NGS on other tumors, and explored TMB in a broad range of SGCs. To our knowledge, this is the largest comparison study of SGC genomics to date.

The key finding of this study is the difference in mutation profile between SGC histotypes more commonly associated with a good prognosis (ACC, AciCC, PLGA, myoepi, and MASC) compared with more clinically aggressive tumors (MEC, SDC, AD-NOS, CA-NOS, Ca ex PA). In particular, less aggressive histotypes had fewer GAs/tumor (2.1 versus 4.3) and less frequent TP53 GAs. Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is extremely common in cancers of all types [11]. Our study found similar ranges to reported TP53 mutation frequency in COSMIC (17%) and other published literature (14%–60% depending upon histotype) [12, 13]. On a more micro level, increasing frequency of TP53 mutations has been implicated in the transition for pleomorphic adenomas to carcinomas and increasing grade of MECs [14, 15]. Based upon these data, typical SGC prognosis may be explained, in part, by underlying mutational complexity.

In this study, more clinically indolent tumors have fewer PIK3CA and ERBB2 GA. PIK3CA GAs range from 0% to 15% in more indolent histologies, less than the aggressive histotypes (20%–27%). While the PIK3CA mutation rate is not known from many SGCs, the PIK3CA mutation rate in among all SGCs in
COSMIC is 10% and among SDCs has been reported between 19% and 30% [12, 16, 17]. Moreover, certain histotypes in this study, such as SDC and AD-NOS, had frequent GAs in other PI3K pathway genes, including PTEN, RICTOR, TSC2, and NF1. The PI3K pathway is involved in myriad cancer-promoting functions and may be targeted by drugs such as everolimus [18, 19]. PI3K pathway inhibitors may be a valuable tool for certain SGCs in the future. Similarly, there were no ERBB2 GAs in the more indolent compared with the significantly higher ERBB2 amplification and SV GA frequencies in several of the more rapidly progressive tumors. Moreover, most (87%) of tumors with ERBB2 GAs also carried a TP53 mutation. The frequency of ERBB2 GAs, particularly in SDCs, is striking, as it has the highest rate of ERBB2 amplification of any tumor [10]. Prior studies have reported frequent HER2 staining or ERBB2 amplification, particularly in more aggressive SGCs [16]. Based upon the patient report in this manuscript and prior reports of responses to HER2 targeted therapy in HER2-positive SGCs [16, 20], we encourage further exploration of HER2 therapy in either basket- or SGC-specific studies.

For the first time, TMB was reported for many SGCs in this study. TMB was lower (<5% of tumors featuring ≥10 mut/Mb) in the more clinically indolent ACC, AciCC, PLGA, myoepi, and MASC groups compared with the more aggressive MEC, SDC, AD-NO, CA-NOS and ca ex PA, though no tumor exceeded 21% frequency for ≥10 mut/Mb. TMB has been linked with benefit from immune checkpoint inhibitors (ICPI) in several cancers [8, 25]. The validated hybrid capture–based NGS platform used in this study to determine the TMB has consistently equaled or outperformed other biomarker assessments for predicting ICPI response and may have the advantage of objectivity over immunohistochemistry for PD-L1 expression [25–27]. For SGCs, the TMB is significantly lower than the tumor types where ICPI are approved such as NSCLC, melanoma, and bladder cancer, where a cut-off of approximately 20 mutations/Mb tends to predict long-term clinical benefit from the ICPI drugs [8, 25, 26]. Early data from the Keynote-028 trials suggest modest activity (11.5% response rate) in non-ACC SGCs treated with pembrolizumab. We look forward to the results of Keynote 158, which enrolled a large number of SGCs.

Table 2. Examples of responses to targeted therapy for salivary gland cancers treated following next-generation sequencing

| SGC type | Genomic alteration | Therapy | Results               |
|----------|--------------------|---------|-----------------------|
| SDC      | ERBB2              | Carboplatin/docetaxel/trastuzumab | Partial response |
| SDC      | NCOA-RET           | Cabozantinib  | Partial response |
| AciCC    | BRAF duplication of exons 10-18 | Regorafenib  | Partial response |
| AciCC    | BRCA2              | Olaparib  | Progressive disease |
| MASC     | ETV6-NTRK3 fusion  | EGFR plus PI3K inhibitor | Minor response, prolonged stable disease |

Figure 2. Computed tomography scans of a patient with mammary analog secretory tumor harboring an ETV6-NTRK3 gene fusion before and after treatment with a PI3K and EGFR inhibitors.

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patient survival are not available. Moreover, certain GAs, such as the MECT1-MAML2 translocation commonly identified in MEC, are not assessed using this technique [28]. Androgen receptor testing, an important tool in SDC diagnosis, is not available using CGP [29]. Lastly, each histologic subtype was group for the purpose this study, though we know tumor grade and mutations can vary within each tumor type, such as MEC [14]. Despite these limitations, this study contributes greatly to the understanding of SGC’s genetic underpinnings.

In summary, this study of >600 clinically relapsed and metastatic salivary gland cancers highlights the potential roles of a hybrid capture based CGP assay to simultaneously differentiate among a wide variety of tumor histologies, identify genomic driver alterations that can be exploited in targeted therapy strategies, and measure the tumor mutational burden to identify potential immune checkpoint inhibitor responsiveness.

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**References**

1. Jones AV, Craig GT, Speight PM, Franklin CD. The range and demographics of salivary gland tumours diagnosed in a UK population. Oral Oncol 2008; 44: 407–417.
2. Jones SJ, Laskin J, Li YY et al. Evolution of an adenocarcinoma in response to selection by targeted kinase inhibitors. Genome Biol 2010; 11: R82.
3. Zarbo RJ. Salivary gland neoplasia: a review for the practicing pathologist. Mod Pathol 2002; 15: 298–323.
4. Amini A, Waxweiler TV, Brower JV et al. Association of adjuvant chemotherapy vs radiotherapy alone with survival in patients with resected major salivary gland carcinoma: data from the National Cancer Data Base. JAMA Otolaryngol Head Neck Surg 2016; 142: 1100–1110.
5. Lagha A, Chretien N, Ayadi M et al. Systemic therapy in the management of metastatic or advanced salivary gland cancers. Oral Oncol 2012; 48: 948–957.
6. Grunewald I, Vollbrecht C, Meinrath J et al. Targeted next generation sequencing of parotid gland cancer uncovers genetic heterogeneity. Oncotarget 2015; 6: 18224–18237.
7. Kato S, Elin SK, Schaererle M et al. Genomic landscape of salivary gland tumors. Oncotarget 2015; 6: 25631–25665.
8. Rizvi NA, Hellmann MD, Snyder A et al. Cancer immunology. Mutualistic landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015; 348: 124–128.
9. Frampton GM, Fichtenholtz A, Otto GA et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol 2013; 31: 1023–1031.
10. Chmielecki J, Ross JS, Wang K et al. Oncogenic alterations in ERBB2/HER2 represent potential therapeutic targets across tumors from diverse anatomic sites of origin. Oncologist 2015; 20: 7–12.
11. Brown CJ, Lain S, Verma CS et al. Awakening guardian angels: dragging the p53 pathway. Nat Rev Cancer 2009; 9: 862–873.
12. Forbes SA, Beare D, Gunasekaran P et al. COSMIC: exploring the world’s knowledge of somatic mutations in human cancer. Nucleic Acids Res 2015; 43: D805–D811.
13. Gomes CC, Diniz MG, Orsine LA et al. Assessment of TP53 mutations in benign and malignant salivary gland neoplasms. PLoS One 2012; 7: e41261.
14. Wang K, McDermott JD, Schrock AB et al. Comprehensive genomic profiling of salivary mucoepidermoid carcinomas reveals frequent RAP1, PIK3CA, and other actionable genomic alterations. Ann Oncol 2017; 28: 748–753.
15. Jaehne M, Roeser K, Jaekel T et al. Clinical and immunohistologic typing of salivary duct carcinoma: a report of 50 cases. Cancer 2005; 103: 2526–2533.
16. Profane K, Russell JS, McDermott JD et al. Profiling of 149 salivary duct carcinomas, carcinoma ex pleomorphic adenomas, and adenocarcinomas, not otherwise specified reveals actionable genomic alterations. Clin Cancer Res 2016; 22: 6061–6068.
17. Kang H, Tan M, Bishop JA et al. Whole-exome sequencing of salivary gland mucoepidermoid carcinoma. Clin Cancer Res 2017; 23: 283–288.
18. Engelma JA. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. Nat Rev Cancer 2009; 9: 550–562.
19. Janku F, Wheler JJ, Naing A et al. PIK3CA mutations in advanced cancers: characteristics and outcomes. Oncotarget 2012; 3: 1566–1575.
20. Limaye SA, Posner MR, Kneiger FE et al. Trastuzumab for the treatment of salivary duct carcinoma. Oncologist 2013; 18: 294–300.
21. Klempner SJ, Bordoni R, Gowen K et al. Identification of BRAF V600E domain duplications across multiple tumor types and response to RAF inhibitor therapy. JAMA Oncol 2016; 2: 272–274.
22. Nardi V, Sadov PD, Juric D et al. Detection of novel actionable genetic changes in salivary duct carcinoma helps direct patient treatment. Clin Cancer Res 2013; 19: 480–490.
23. Skalova A, Vanecek T, Sima R et al. Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a hitherto undescribed salivary gland tumor entity. Am J Surg Pathol 2010; 34: 599–608.
24. Rehbele RC, Davis LE, Vaishnavi A et al. An oncogenic NTRK fusion in a patient with soft-tissue sarcoma with response to the tropomyosin-related kinase inhibitor LOXO-101. Cancer Discov 2015; 5: 1049–1057.
25. Johnson DB, Frampton GM, Riith MJ et al. Targeted next generation sequencing identifies markers of response to PD-1 blockade. Cancer Immunol Res 2016; 4: 959–967.
26. Rosenberg JE, Hoffman-Censits J, Powles T et al. Atezolizumab in patients with advanced non-small-cell lung cancer expressing PD-L1. N Engl J Med 2016; 375: 1829–1840.
27. Hansen AR, Siu LL. PD-L1 Testing in Cancer: Challenges in Companion Diagnostic Development. JAMA Oncol 2016; 2: 15–16.
28. Nordkvist A, Gustafsson H, Julberg-Ode M, Stenman G. Recurrent rearrangements of 11q14-13 in mucoepidermoid carcinoma. Cancer Genet Cytogenet 1994; 74: 77–83.
29. Cros J, Sbidian E, Hans S et al. Expression and mutational status of treatment-relevant targets and key oncopgenes in 123 malignant salivary gland tumours. Ann Oncol 2013; 24: 2624–2629.