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ORIGINAL ARTICLE

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

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 (AciCC), 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 adenomas (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, AciCC, 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 ductal 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 cancers, 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 *PDGFRA* and *KIT*, was low with no major genomic target present in greater than 5% of cases. AciCC: 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 *NF1* (5%). PLGA: There were 1.6 GA/tumor with only a single potentially targetable GA in *PTEN* (Table 1; Figure 1C). Myoepit: 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 (*PDGFRB*) (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	4.2	3.6	4.1	5.2	3
Median age in years	55	55	72	56	62	58	67	61	63	62
Gender (% female/% male)	50% F 50% M	54% F 46% M	80% F 20% M	42% F 58% M	38% F 62% M	46% F 54% M	18% F 82% M	26% F 74% M	35% F 65% M	50% F 50% M
Significant GAs (%)	MYB-NFIB (65)	PTEN (10) BRAF (5) NF1 (5)	PTEN (20) TSC2 (20) FGFR1 (20)	PIK3CA (15) RICTOR (15) PTCH1 (10) PDGFRB (5)	ETV6-NTRK3 (100)	PIK3CA (20) ERBB2 (13) BRCA2 (17) FGFR1 (7)	ERBB2 (32) PTEN 17) BRAF (5) PIK3CA (27)	ERBB2 (17) BRAF (5) EGFR (5) PIK3CA (24)	ERBB2 (15) PIK3CA (20) NF1 (8) PTEN (8) NF1 (8)	ERBB2 (32) 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 >10 mut/Mb (%)	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.

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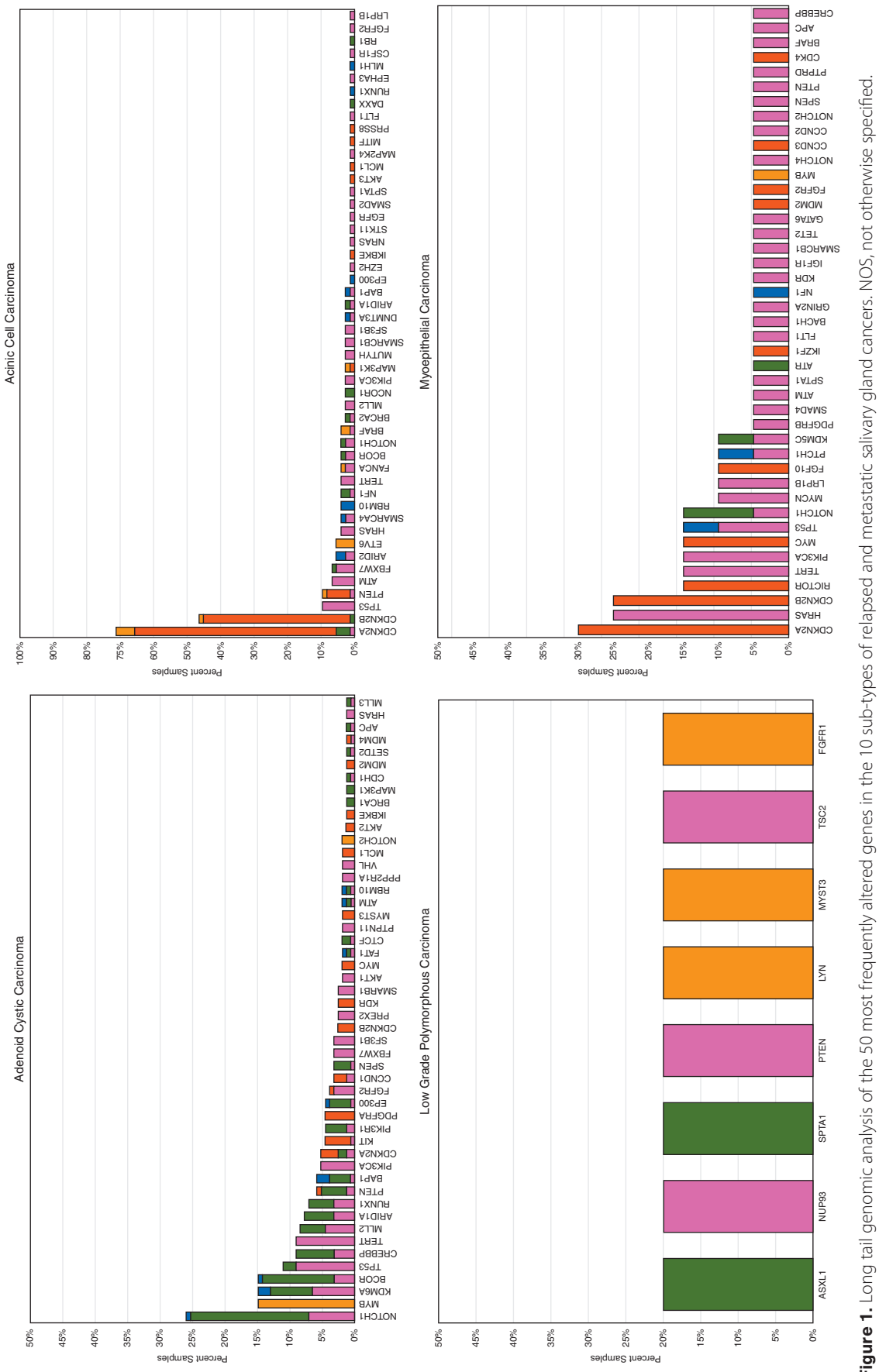
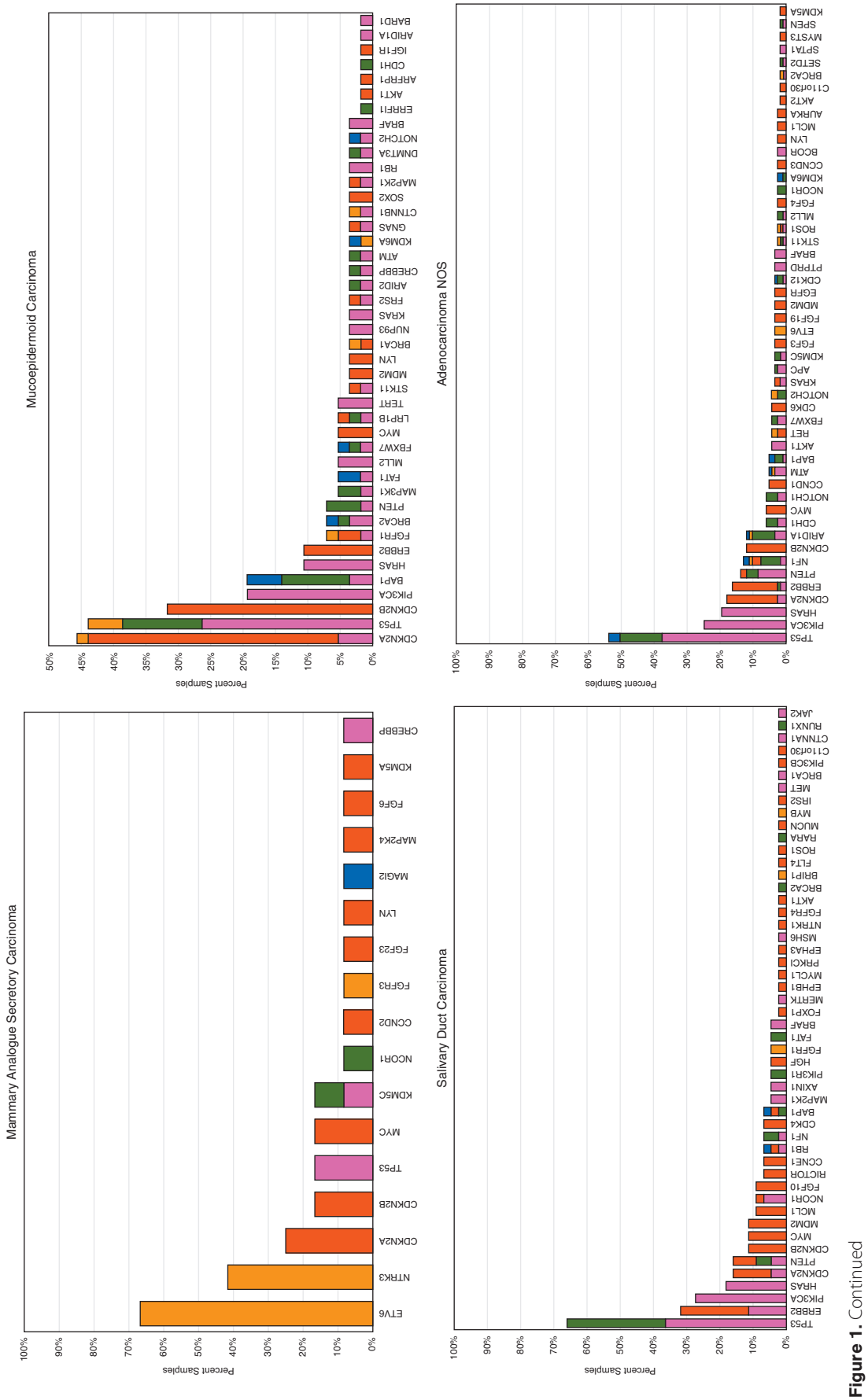


Figure 1. Long tail genomic analysis of the 50 most frequently altered genes in the 10 sub-types of relapsed and metastatic salivary gland cancers. NOS, not otherwise specified.



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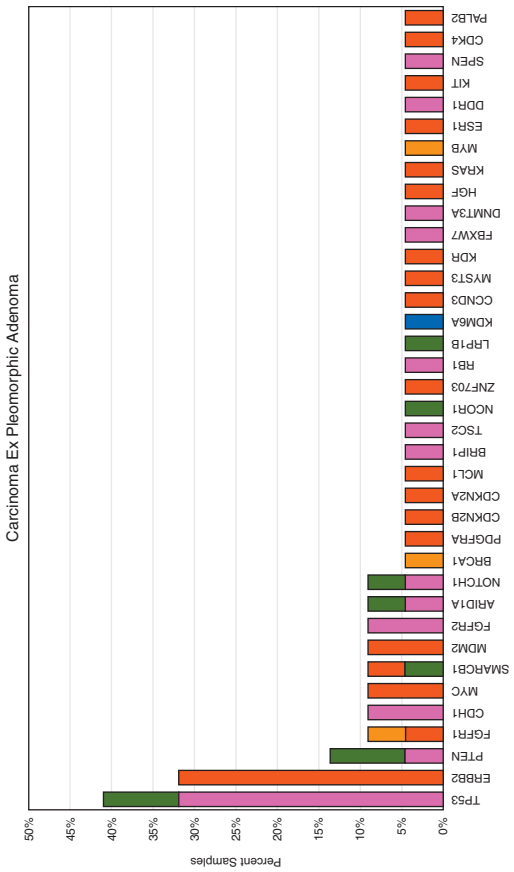

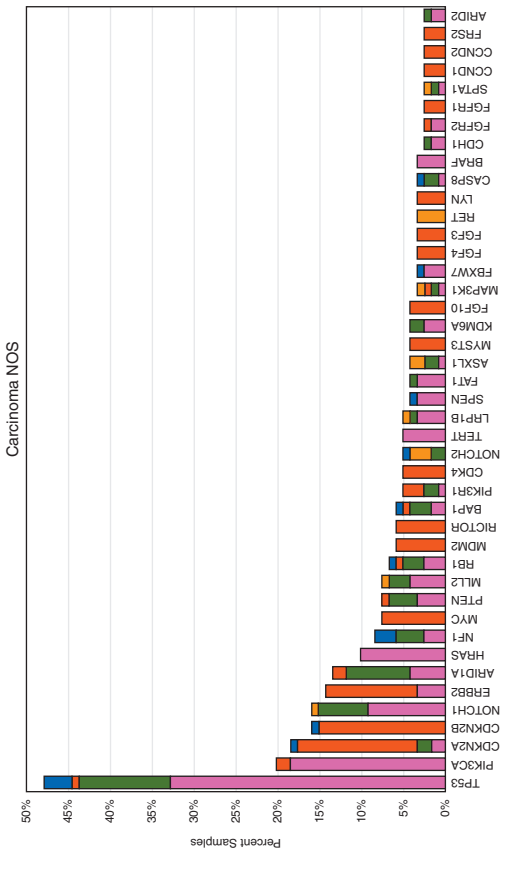

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(17%), *RICTOR* and *CDK4* (7%), *FGFR1* and *BRAF* (5%), and *RET* (2%). Interestingly, only one *ERBB2* amplified SDC harbored a *PIK3CA* mutation (Table 1; Figure 1H). AD-NOS: The median GA/tumor was 4.1. Interesting GAs included *EGFR* (5%) (Table 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 1J). 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

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

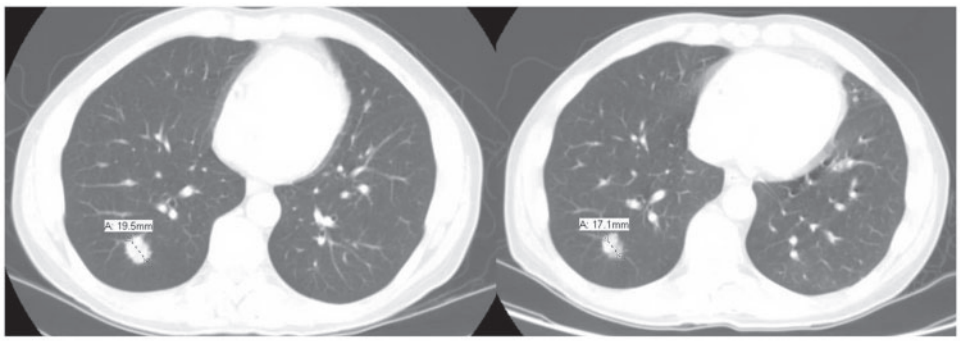

Figure 2. Computed tomography scans of a patient with mammary analog secretory tumor harboring an *ETV6-NTRK3* gene fusion before and after treatment with a PI3K and EGFR inhibitors.

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.

This study identified other noteworthy genomic targets in a wide range of SGCs. For instance, though *BRAF* mutations were not common in this study, they did tend to be activating and one AciCC patient with a *BRAF* gene fusion responded to a multikinase inhibitor targeting BRAF [21]. The *BRAF* GA rate in this study (2.7%) was similar to the 2% observed in COSMIC, though the rate reported here is a little lower than that reported in another SDC study [12, 22]. Consistent with other studies, this study found frequent *MYB-NFIB* fusions in ACC and supported that *ETV6-NTRK3* fusions are characteristic of MASCs [23]. In particular, the demonstration of *ETV6-NTRK3* fusions in SGCs is critical, as novel TRK inhibitors have started to demonstrate efficacy in cancers harboring *NTRK3* fusions [24]. Beyond these, infrequent GAs were seen in potentially targetable genes such as *RET, BRCA1/2, FGFR*, and *PDGFR*. We believe CGP may allow for common and rare therapeutic targets to be identified in these difficult to treat cancers.

For the first time, TMB was reported for many SGCs in this study. TMB was lower ($\leq$5% of tumors featuring $\geq$ 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 $\geq$ 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.

While this study has many strengths, there are limitations. The greatest weakness is the lack of clinical correlations between identified GAs and disease characteristics or patients outcomes. As this was a retrospective evaluation of samples submitted for clinical care, data about cancer stage, response to therapies, and

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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