

Review

## Mutational Signatures in Salivary Gland Carcinomas

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**Abstract.** Salivary gland carcinomas belong to the head and neck carcinoma super category of malignancies. They are characterized by histopathological diversity and comprise a variety of entities and subtypes. Mucoepidermoid, adenoid cystic and salivary duct carcinomas represent the most prominent malignancies. Concerning their corresponding genetic background, a broad spectrum of gene and chromosomal imbalances has been detected. Point mutations and deletions, amplifications and translocations, combined or not with chromosomal aneuploidy/polysomy/monosomy, create a landscape of specific genetic signatures that affect the

biological behavior of these tumors and modify response rates to potential targeted therapeutic strategies. In the current molecular review, we focused on the categorization and description of the most important mutational signatures in salivary gland carcinomas.

Cancerous tissues exhibit a broad spectrum of genetic and epigenetic imbalances, including gross (chromosomal instability) or specific gene alterations (1). More specifically, numerical gene imbalances refer mainly to amplifications (gene-copy gains) or deletions (loss or silencing of allele/s), whereas gene structural modifications include translocations (rearrangements and fusions) (2). Histopathological changes in normal epithelia are reflections of these genetic modifications at the molecular level that create the corresponding cancer-related genomes (3). Among the head and neck carcinoma super family of malignancies, neoplasms derived from salivary gland epithelia form a specific group of solid tumors with distinct histopathological and genetic profiles (4). Concerning the anatomical location and structure of normal salivary glands, there are two main types: the major and the minor. The first category comprises the parotids, submandibular, and sublingual glands, whereas the second category includes the very small ones that are situated on the tongue, lips nose, sinuses, mouth, and larynx (5). In the current review, we explored the correlation

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Table I. Mutated/deleted genes found in salivary gland carcinoma (SGC) variant.

SGC type	Gene altered										
	<i>TP53</i>	<i>HRAS</i>	<i>PIK3CA</i>	<i>NOTCH1</i>	<i>PRKD1</i>	<i>TP63</i>	<i>CDKN2A*</i>	<i>ERBB2</i>	<i>CTNBI</i>	<i>CYLD</i>	<i>PTEN*</i>
MEC			X				X				
ADCC				X		X					
SDC	X	X	X				X				X
CexPA	X										
EMC		X									
TBCAC									X		
MBCA										X	
PAC					X						
CAMSG					X						
IDC		X	X								
MAC	X										
OSGC								X			

ADCC: Adenoid cystic carcinoma; CAMSG: cribriform adenocarcinoma of (minor) salivary gland; CexPA: carcinoma ex pleomorphic adenoma; EMC: epithelial–myoepithelial carcinoma; IDC: intraductal carcinoma; MAC: mucinous adenocarcinoma; MBCA: membranous basal cell adenoma; MEC: mucoepidermoid carcinoma; OSGC: oncocytic salivary gland carcinoma; PAC: polymorphous adenocarcinoma; SDC: salivary duct carcinoma; TBCAC: tubulotrabeular basal cell adenocarcinoma. Genes: *CDKN2A*: cyclin-dependent kinase inhibitor 2A; *CTNBI*: catenin beta 1; *CYLD*: CYLD lysine 63 deubiquitinase; *ERBB2*: erb-b2 receptor tyrosine kinase 2; *HRAS*: HRas proto-oncogene, GTPase; *NOTCH1*: notch receptor 1; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; *PRKD1*: protein kinase D1; *PTEN*: phosphatase and tensin homolog; *TP53*: tumor protein 53; *TP63*: tumor protein 63. \*Deletion.

between histopathological and genetic features of salivary gland carcinomas (SGCs) by presenting and describing the most important mutational signatures found in them.

### SGCs: Histopathological Subtypes and Chromosomal Imbalances

According to the updated World Health Organization classification, SGCs comprise main, secondary, and rare histological subtypes (6). Mucoepidermoid (MEC), adenoid cystic (ADCC) and salivary duct (SDC) carcinomas represent the most significant sub-categories. MECs are mainly well- and moderately-differentiated carcinomas derived predominantly from the parotid glands (7). ADCC is the second most frequently detected carcinoma in all major glands, mainly being well differentiated, but also being characterized by elevated rates of recurrence after surgical excision and radiation-based treatment (8). SDC is a high-grade malignancy with increased metastatic potential and poor prognosis, affecting mainly the parotid glands and demonstrating rapid growth as a neck mass (9). Acinic-cell carcinoma, secretory carcinoma, polymorphous adenocarcinoma, basal cell adenocarcinoma, clear-cell carcinoma, cystadenocarcinoma, sebaceous adenocarcinoma, sebaceous lymphadenocarcinoma, and mucinous adenocarcinoma are significant but less frequent subtypes of SGCs (10). Additionally, carcinoma ex pleomorphic adenoma, carcinosarcoma, squamous cell carcinoma, epithelial–myoepithelial carcinoma, intraductal carcinoma, secretory

carcinoma, anaplastic small cell carcinoma, and undifferentiated carcinomas are rare or very rare but most aggressive regarding their biological behavior (11).

Chromosomal instability – as a result of gross numerical chromosomal alterations including gains (polysomy) or losses (monosomy) – is involved in the majority of the previously referred pathological SGC variants, combined with specific gene alterations (12). Some cytogenetic analyses have reported that SDC is characterized by gene alterations on chromosome 17, adenoid cystic carcinoma demonstrates alterations in chromosomes 6, 8, and X, whereas chromosomes 9, 11, 15, and 19 are implicated in the onset and development of MEC (13, 14). Furthermore, in basal cell carcinoma, genes on chromosome 16 are deregulated, carcinoma ex pleomorphic adenoma demonstrates chromosome 8 and 12 imbalances, whereas the genetic profile of polymorphous adenocarcinoma comprises alterations in chromosomes 1, 2, 14, 19 and X (15, 16). In other rare histopathological entities, such as secretory and clear-cell carcinoma, gene imbalances on chromosomes 12, 15, and 22 have been identified (17).

### Mutational Signatures in SGCs

Concerning SGC variants, molecular analyses based on polymerase chain reaction and novel next-generation sequencing techniques have revealed differences regarding their mutational profiles and the frequency of the detected mutations (approximately 10-75% in the corresponding

genes) (18, 19) (Table I). More specifically, mutations in phosphoprotein 53 tumor-suppressor gene (*TP53*: 17p13) have been detected in SDC and carcinoma ex pleomorphic adenoma and were correlated with an aggressive phenotype (increased stage and metastatic potential, and poor prognosis in a subgroup of cases) (20-22). In SDC and intra-ductal carcinoma, mutations have also been detected in another critical oncogene, that of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*: 3q26) (23). The gene encodes for the p110 alpha protein that activates the catalytic unit of the PI3K enzymatic factor. Additionally, deletion in the suppressor gene phosphatase and tensin homolog (*PTEN*: 10q23) has also been detected. Epithelial–myoepithelial variant of SGC frequently harbors point mutations of the HRas proto-oncogene, GTPase (*HRAS*: 11p15), an oncogene belonging to the RAS super family of genes that encodes for a GTPase enzyme, the cell-cycle regulator p21 protein (24, 25). ADCC is characterized by mutations in a specific gene, the notch receptor 1 (*NOTCH1*: 9q34) that encodes for a single-pass transmembrane receptor (26, 27). Interestingly, other specific SGC entities, such as polymorphous adenocarcinoma and cribriform adenocarcinoma, exhibit mutations in the protein kinase D1 gene (*PRKD1*: 14q12) (28-30). The corresponding protein product is a serine-threonine protein kinase implicated in cell migration, tissue differentiation, and signaling transduction in the mitogen-activated protein kinase/extracellular-regulated kinase pathway.

Besides the previous referred distinct mutational signatures that are almost exclusively detected in the corresponding histotypes, there are rare cases that demonstrate differences or a combination of them. A study group analyzing a series of MECs detected synchronous mutations affecting *PIK3CA* and deletions in cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*: 9p21) genes, respectively (31). The latter encodes for the p16 and p14 suppressor proteins involved in regulation of cell-cycle progression and it has been found to be mutated/deleted in subsets of MECs. Furthermore, another molecular study based on the analysis of an ADCC series revealed two genetically distinct categories: ADCC-I and II. ADCC-I is characterized by *NOTCH1* mutations that activate the MYC-dependent signaling transduction pathway, whereas ADCC-II exhibits overexpression of tumor protein 63 (*TP63*: 3q28) (32). The latter gene encodes a strong transcription factor. Synchronous mutation of *TP53*, *PIK3CA* and *HRAS* combined with *CDKN2A* deletions has also been identified in subsets of SDCs (33).

Another interesting parameter regarding the mutational landscape of SGCs is the role of epidermal growth factor receptor type 2 (*HER2/ERBB2*: 17q21) alterations. Although the main mechanism of deregulation of this gene is still amplification (production of multiple gene copies on chromosome 17 that leads to its protein overexpression), there

are some studies supporting the idea that the gene is mutated in some cases. In one of them, the study group detected synchronous *TP53* and *ERBB2* mutations in a series of oncocytic SGCs, which represent a distinct histopathologically and molecularly heterogeneous group inside the SGC super family (34). Similarly, another genetic analysis showed differences in *ERBB2* mutation/amplification status regarding a series of solid malignancies analyzed, including SGCs (35). Finally, two more genes, the catenin beta 1 gene (*CTTNB1*: 3p22) encoding a significant cell-to-cell adhesion molecule acting as a cadherin-associated factor, and *CYLD* lysine 63 deubiquitinase (*CYLD*: 16q12) gene, encoding a strong protease, have been found to be mutated in tubulotrabeular basal cell and membranous basal cell adenomas and adenocarcinomas of salivary glands (36, 37).

In conclusion, SGCs represent a broad spectrum of solid malignancies derived from salivary glands and stroma, characterized by histogenetic differences. According to their categorization, each variety demonstrates specific mutational signatures affecting mainly *TP53*, *HRAS*, *NOTCH1*, *PIK3CA* and *CDKN2*, and to a lesser extent *ERBB2*, *TP63*, *PRKD1*, *CYLD* and *CTTNB1* genes. Based on these individually or their combination in some cases, oncologists hope to develop and apply targeted therapeutic regimens in order to manage subgroups of patients to improve response rates and survival prognosis.

## Conflicts of Interest

The Authors have no conflicts of interest to declare.

## Authors' Contributions

ET, AC, and VP: Design of the study and article writing; DS, DP, VR, NM and EK: academic advisors; PP, AA, SP, DR, GP and SM: collection and management of references and published data. All Authors read and approved the final article.

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