Molecular Pathology
Predictive, Prognostic, and Diagnostic Markers in Salivary Gland Tumors

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KEYWORDS

• Salivary • Molecular • Translocations • Mutations • Classification

Key points

- Recognition of defining molecular alterations, usually translocations, in monomorphic salivary gland tumors has emerged as a paradigm for tumor diagnosis.
- Proper front-end traditional morphologic and immunophenotypic characterization improves the impact of the complex alterations seen in pleomorphic high-grade salivary carcinomas.
- Mucoepidermoid carcinoma, adenoid cystic carcinoma, mammary analog secretory carcinoma, and hyalinizing clear cell carcinomas harbor translocations that are readily testable by fluorescence in situ hybridization.
- Salivary duct carcinoma is defined by an apocrine phenotype.
- The taxonomy of polymorphous low-grade adenocarcinoma and cribriform adenocarcinoma of salivary gland is currently debated and has recently incorporated the findings of next-generation sequencing identifying reproducible mutations and translocations in the *PRKD* family of genes.

ABSTRACT

Although initial attempts at using ancillary studies in salivary gland tumor classification were viewed with skepticism, numerous advances over the past decade have established a role for assessment of molecular alterations in the diagnosis and potential prognosis and treatment of salivary gland tumors. Many monomorphic salivary tumors are now known to harbor defining molecular alterations, usually translocations. Pleomorphic, high-grade carcinomas tend to have complex alterations that are often further limited by inaccuracy of initial classification by morphologic and immunophenotypic features. Next-generation sequencing techniques have great potential in many aspects of salivary gland tumor classification and biomarker discovery.

OVERVIEW

Salivary gland tumors are rare but morphologically diverse. The significant histologic overlap between tumor types with different biological behavior not only poses diagnostic challenges but also colored early attempts at using ancillary studies to refine diagnoses with a good deal of skepticism. However, the ensuing decades bore witness to significant refinements of morphologic criteria, developments of newer immunohistochemical markers, and the discovery of key molecular alterations in a variety of different tumor types. The initial defeatist attitude towards ancillary testing in salivary gland tumors has been slowly replaced with a more optimistic, integrative mindset. Although morphologic features remain the cornerstone of salivary gland tumor assessment, ancillary testing can now help refine diagnosis, and in

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some instances provide prognostic and predictive value.

ASSOCIATED GENETIC CHANGES/ ALTERATIONS

Given the rarity of salivary gland tumors, the molecular understanding of these tumors was initially slow to evolve. Limitations have included a scarcity of in vitro and animal models and paucity of high-quality clinical annotation, limiting the relevance of any molecular alterations. Hereditary associations and precursor lesions are rare. Importantly, many tumor types are consistently misdiagnosed, which affects the accuracy of the available molecular findings. **Table 1** summarizes current key molecular alterations in salivary gland tumors.

DIAGNOSIS-DEFINING MOLECULAR ALTERATIONS: A NEW PARADIGM IN MONOMORPHIC SALIVARY GLAND TUMORS

One of the earliest reproducible translocations in salivary gland tumors, the t(11;19) in mucoepidermoid carcinoma, was discovered in 1994 by conventional karyotyping,[1] but it was nearly a decade later that the translocation partners *CRTC1* (*MECT1*) and *MAML2* were resolved.[2] In the following 5 to 10 years the diagnostic and prognostic uses and limitations of this translocation were established.[3–6] Now, mucoepidermoid carcinoma is regarded as one of the first to exemplify a new paradigm in monomorphic salivary gland tumors; namely that there is a high likelihood of a reproducible genetic alteration defining these tumors. Adenoid cystic carcinoma shares a similar story with mucoepidermoid carcinoma and is often characterized by an *MYB-NFIB* translocation.[7] Some consistent alterations were already established, notably *PLAG1* and *HMGA2* translocations in pleomorphic adenomas,[8,9] but largely ignored given that they characterized a benign tumor.

Other more recent diagnosis-defining translocations were established with a mixture of serendipity and astute correlation with the morphologic features of entities at other sites. For instance, *ETV6-NTRK3*–translocated

Table 1
Key molecular alterations in salivary gland tumors

Tumor	Chromosomal Alteration	Gene	Prevalence (%)
Pleomorphic adenoma	8q12 12q13–15 rearrangements	*PLAG1* *HMGA2*	25–30 10–15
Epithelial-myoepithelial carcinoma	11p15.5	*HRAS*	25
Tubulotrabecular basal cell adenoma/adenocarcinoma	3p22.1	*CTTNB1* mutation	60–70
Membranous basal cell adenoma/adenocarcinoma	16q12–13	*CYLD1* loss of heterozygosity/mutation	75–80
Mucoepidermoid carcinoma	t(11;19)(q21;p13) t(11;15)(q21;q26)	*CRTC1-MAML2* *CRTC3-MAML2*	40–80 ~5
Salivary duct carcinoma	17q21.1 3q26.32	*ERBB2* amplification *PIK3CA* mutation	~40 ~20
Adenoid cystic carcinoma	t(6;9)(q22–23;p23–24)	*MYB-NFIB*	25–50
Mammary analogue secretory carcinoma	t(12;15)(p13;q25) t(12;XXX)	*ETV6-NTRK3* *ETV6-XXX*	~95–98 (defining) ~2–5 (defining)
Hyalinizing clear cell carcinoma	t(12;22)(q21;q12)	*EWSR1-ATF1*	~80–90 (defining)
Myoepithelial carcinoma	t(22;XXX)	*EWSR1-XXX*	~40 clear cell morphology 0 non–clear cell morphology
Polymorphous low-grade adenocarcinoma/Cribriform adenocarcinoma of minor salivary origin	14q12 t(1;14)(p36.11;q12) t(X;14)(p11.4;q12)	*PRKD1* mutation *ARID1A-PRKD1* *DDX3X-PRKD1* *PRKD2* rearrangement *PRKD3* rearrangement	~20 ~24 ~13 ~16