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# GATA3 Immunohistochemical Expression in Salivary Gland Neoplasms

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**Abstract** GATA3 is a zinc finger transcription factor that regulates the normal development of many tissues and cell types. Recent studies have shown that immunohistochemical nuclear staining for GATA3 among tumors is highly restricted to carcinomas of breast and urothelial origin; however salivary gland tumors have not been tested. Given that breast and salivary gland tissues are very similar with respect to embryologic development and structure, we performed GATA3 staining on a spectrum of salivary gland neoplasms. GATA3 immunohistochemistry was performed on a diverse collection of 180 benign and malignant salivary gland neoplasms including 10 acinic cell carcinomas, 2 adenocarcinomas not otherwise specified, 41 adenoid cystic carcinomas, 2 epithelial-myoepithelial carcinomas, 1 low grade cribriform cystadenocarcinoma, 15 mammary analogue secretory carcinomas, 7 metastatic squamous cell carcinomas, 27 mucoepidermoid carcinomas, 2 oncocytic carcinomas, 5 oncocytomas, 34 pleomorphic adenomas, 4 polymorphous low grade adenocarcinomas, 25 salivary duct carcinomas, and 5 Warthin tumors. Staining for GATA3 was observed in 92/180 (51 %) of salivary gland tumors. GATA3 staining was observed in most of the tumor types, but diffuse immunolabeling was consistently seen in salivary duct carcinoma (25 of 25) and mammary analogue secretory carcinoma (15 of 15)—the two tumor types that most closely resemble breast neoplasia. Background benign salivary gland tissue was also usually weakly positive in both acini and ducts. GATA3 immunostaining is not restricted to tumors of breast and urothelial origin. Rather, it is expressed across many different types of salivary gland neoplasms. As a result, salivary gland origin should be considered in the differential diagnosis of a GATA3-positive carcinoma, particularly in the head and neck. Although GATA3 immunohistochemistry is not helpful in resolving the differential diagnosis between a primary salivary gland neoplasm and metastatic breast cancer, it may have some utility in subtyping salivary gland tumors, particularly salivary duct carcinoma and mammary analogue secretory carcinoma.

**Keywords** GATA3 · Immunohistochemistry · Salivary glands · Salivary duct carcinoma · Mammary analogue secretory carcinoma

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## Introduction

GATA binding protein 3 (GATA3) is a member of the GATA family of zinc finger transcription factors that regulate the normal development of various tissue and cell types including breast [1, 2], T-lymphocytes [3], kidney [4, 5], nerve [6], and skin [7]. Recent studies have proposed that immunohistochemical nuclear staining for GATA3 in tumors is mostly restricted to neoplasms of breast and urothelial origin [8, 9]. Accordingly, GATA3 immunohistochemical staining is being used as a practical tool for

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diagnosing breast and urothelial carcinoma, particularly when these tumors present as distant metastases or are so poorly differentiated that they cannot be distinguished from other tumor types [10–12]. Various studies across a broad spectrum of diverse tumor types have confirmed the restricted expression of GATA3 staining to breast and urothelial origin, but these studies have curiously not included salivary gland neoplasms [1–12]. Mammary glands and salivary glands are both ectodermally-derived exocrine secretory structures that share many embryologic, histologic, and immunohistochemical features. The purpose of this study was to determine the presence and distribution of GATA3 staining across a diverse group of salivary gland neoplasms.

## Design

Unstained slides from 180 salivary gland tumors were retrieved. One hundred twenty-two of the neoplasms were present in previously constructed tissue microarrays, and 58 tumors were on whole slides. The primary salivary gland tumors studied included adenoid cystic carcinomas (n = 41), pleomorphic adenomas (n = 34), mucoepidermoid carcinomas (n = 27), salivary duct carcinomas (n = 25), mammary analogue secretory carcinomas (n = 15), acinic cell carcinomas (n = 10), oncocytomas (n = 5), Warthin tumors (n = 5), polymorphous low grade adenocarcinomas (n = 4), adenocarcinomas not otherwise specified (n = 2), epithelial-myoepithelial carcinomas (n = 2), oncocytic carcinomas (n = 2), and low grade cribriform cystadenocarcinoma (n = 1). The mammary analogue secretory carcinomas were classified according to the histologic and molecular criteria set forth by Skalova et al. [13] in the initial description of that entity. Indeed, each case was proven to harbor an *ETV6* rearrangement by fluorescent in situ hybridization, as previously reported [14, 15].

GATA3 immunohistochemistry (1:100 dilution; clone L50-823; Biocare Medical, Concord, CA) was performed on each of the 4 micrometer thick sections on a Benchmark XT automated slide stainer (Ventana Medical Systems, Inc. Tucson AZ). The pattern of nuclear staining for each tumor was recorded. Both intensity (weak, moderate, and strong) and extent (% of tumor nuclei positive) of staining was recorded. Positivity in $\geq$50 % of tumor cells was considered diffuse, while staining in <50 % of tumor cells was regarded as focal.

## Results

The results are summarized in Table 1. Staining for GATA3 was observed in 92 of 180 (51 %) salivary gland tumors. GATA3 positivity was consistently present in salivary duct carcinoma (25 of 25, 100 %) and mammary analogue secretory carcinoma (15 of 15, 100 %), two tumor types that exhibit significant morphologic overlap with in situ and infiltrating ductal carcinoma of the breast and secretory breast carcinoma, respectively. In these tumors, GATA3 staining was strong in 26 of 40 (65 %) cases, and it was diffuse in 39 of 40 (98 % cases) (Fig. 1). GATA3 immunoexpression was not limited to those salivary gland tumors with a breast counterpart. GATA3 staining was also present in 1 of 10 (10 %) acinic cell carcinomas (Fig. 2a, b), 9 of 41 (22 %) adenoid cystic carcinomas (Fig. 2c, d), 1 of 2 (50 %) epithelial-myoepithelial carcinomas, 6 of 7 (86 %), 11 of 27 (41 %) mucoepidermoid carcinomas, 1 of 2 (50 %) oncocytic carcinomas, 5 of 5 (100 %) oncocytomas, 13 of 34 (38 %) pleomorphic adenomas (Fig. 2e, f) and 5 of 5 (100 %) Warthin tumors (Fig. 2g, h). The intensity and extent of staining in these tumors was highly variable (Table 1). In the GATA3-positive pleomorphic adenomas, adenoid cystic carcinomas and epithelial-myoepithelial carcinomas, GATA3 was present in both ductal and myoepithelial cells. GATA3 staining was not observed in any of the polymorphous low grade adenocarcinomas (n = 4), adenocarcinomas not otherwise specified (n = 2), or and the low grade cribriform cystadenocarcinoma (n = 1). The background non-neoplastic salivary gland tissue was usually weakly to moderately GATA3 positive in both acini and ducts (Fig. 2c, d).

## Discussion

GATA3 is a transcription factor that regulates the normal development of a variety of tissues. Initial studies demonstrated that GATA3 immunostaining was seen in a limited number of tumor types: mammary carcinoma, urothelial carcinoma, and a minority of endometrial carcinomas [8, 9, 16]. Subsequent studies have expanded the list of GATA3-positive tumors to include occasional squamous cell carcinomas of the anus, cervix, and lung [11, 12]. By performing immunohistochemistry on a large and diverse collection of salivary gland tumors, we found that approximately half were immunoreactive for GATA3. This result is not altogether unexpected considering the well-recognized functional and histologic similarities between normal and neoplastic mammary and salivary glands [17]. Indeed, gross cystic disease fluid protein (GCDFP), another marker of mammary carcinomas, has previously been shown to be positive in up to 41 % of salivary gland tumors [18, 19].

The salivary glands must now be recognized as a possible site of tumor origin for a GATA3-positive carcinoma, particularly in the head and neck. To that end, GATA3 has no role in differentiating carcinomas of breast and salivary gland

**Table 1** Immunoexpression of GATA3 in salivary gland neoplasms

| Tumor type | GATA3 staining (%) | Notes |
|---|---|---|
| Acinic cell carcinoma | 1/10 (10) | Weak to moderate staining in 30 % of cells in the one positive case |
| Adenocarcinoma, NOS | 0/2 (0) | |
| Adenoid cystic carcinoma | 9/41 (22) | Variable strength and intensity |
| Epithelial-myoepithelial carcinoma | 1/2 (50) | Strong staining in 30 % of cells in one positive case |
| Low grade cribriform cystadenocarcinoma | 0/1 (0) | |
| Mammary analogue secretory carcinoma | 15/15 (100) | 14 were diffuse (70–100 %) and 9 were strong |
| Metastatic squamous cell carcinoma | 6/7 (86) | Variable strength and intensity |
| Mucoepidermoid carcinoma | 11/27 (41) | Variable strength and intensity |
| Low grade | 8/14 (57) | |
| Intermediate grade | 1/8 (13) | |
| High grade | 2/5 (40) | |
| Oncocytic carcinoma | 1/2 (50) | Weak in 10 % in the one positive case |
| Oncocytoma | 5/5 (100) | Diffuse (50–100 %) with variable strength |
| Pleomorphic adenoma | 13/34 (38) | Generally weak, variable extent |
| Polymorphous low grade adenocarcinoma | 0/4 (0) | |
| Salivary duct carcinoma | 25/25 (100) | Diffuse (50–100 %) and usually strong (17 cases) |
| Warthin tumor | 5/5 (100) | Diffuse (50–100 %) and usually weak or moderate |
| Total | 92/180 (51) | |

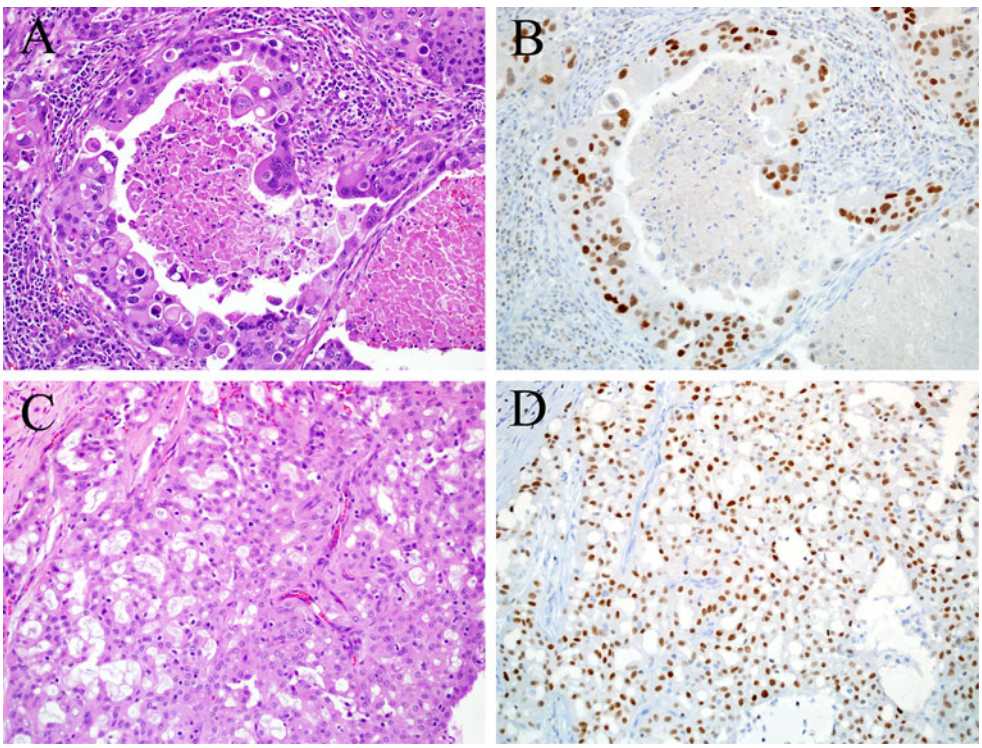


**Fig. 1** GATA3 immunohistochemistry was positive in all cases of salivary duct carcinoma (**a**, **b**) and mammary analogue secretory carcinoma (**c**, **d**), usually in a diffuse and strong fashion

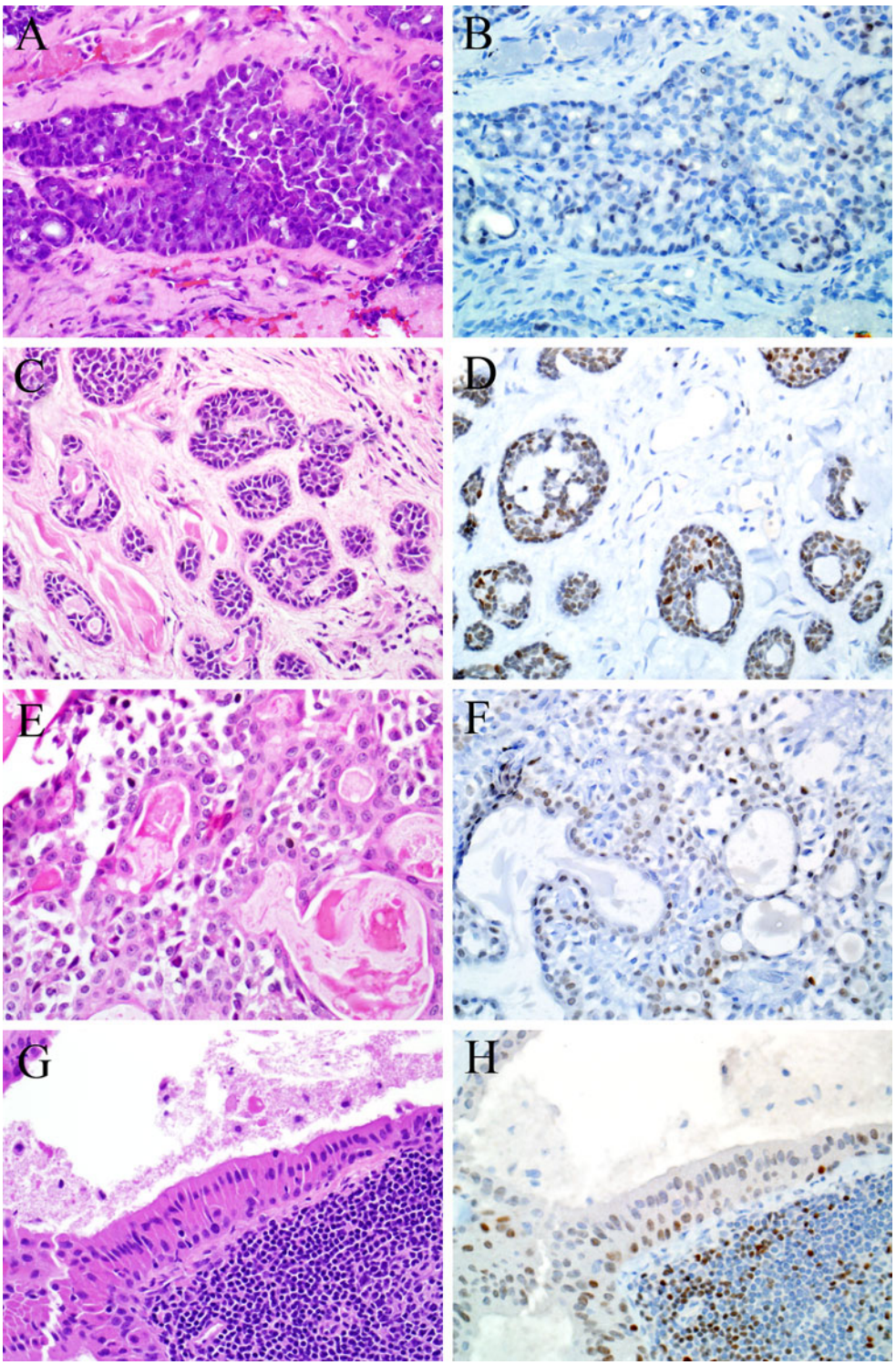


**Fig. 2** GATA3 immunohistochemistry was positive to varying degrees in some cases of malignant tumors such as acinic cell carcinoma (**a**, **b**) and adenoid cystic carcinoma (**c**, **d**) as well as benign tumors such as pleomorphic adenoma (**e**, **f**) and Warthin tumor (**g**, **h**)

origin. For instance, in a salivary gland carcinoma that has features of breast cancer, GATA3 positivity does not exclude a salivary gland primary. Similarly, GATA3 staining in a salivary-type carcinoma of the breast (e.g., adenoid cystic carcinoma) does not confirm mammary gland origin. Indeed, in such circumstances a good clinical history is the most helpful in differentiating primary from metastatic disease. Fortunately, instances of metastatic carcinoma from the breast to the salivary glands and vice versa without a history of a prior or concurrent primary malignancy are very rare [20].

In some circumstances GATA3 immunostaining may be useful in subtyping salivary gland tumors. GATA3 was 100 % sensitive for two carcinomas—salivary duct carcinoma and mammary analogue secretory carcinoma—that are morphologically similar to forms of breast carcinoma and staining was almost diffuse and was usually strong in these tumors. As a result, in a salivary gland tumor that has features of either of those entities, the presence of GATA3 staining is supportive and its absence should give one pause in making the diagnosis. In addition, GATA3 was generally negative in the closest mimickers of mammary analogue secretory carcinoma: acinic cell carcinoma (only one case was focally positive), low grade cribriform cystadenocarcinoma (one case tested was negative), and polymorphous low grade carcinoma (all cases negative). GATA3 may also be useful in distinguishing salivary duct carcinoma from oncocytic carcinoma, which was only focally and weakly positive in one case. One potential pitfall in using GATA3 in the diagnosis of salivary duct carcinoma, however, is that staining may also be seen in high grade mucoepidermoid carcinoma. Careful attention to histologic features—including cribriform architecture with comedonecrosis in salivary duct carcinoma and squamoid cells with mucocytes in high grade mucoepidermoid carcinoma—should resolve the differential diagnosis in most cases.

In summary, the immunoexpression of GATA3—a marker of breast and urothelial carcinoma—is also relatively common in salivary gland tumors. As a result, GATA3 positivity in a tumor of the head and neck is suggestive of salivary gland origin. In particular, GATA3 staining is consistently seen in salivary duct carcinoma and mammary analogue secretory carcinoma, but may also be observed in a number of other salivary gland tumor types.

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