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GATA-3 EXPRESSION IN TROPHOBLASTIC TISSUES: An Immunohistochemical Study of 445 Cases, Including Diagnostic Utility

Natalie Banet, M.D.¹, Allen M. Gown, M.D.², Ie-Ming Shih, M.D., Ph.D.^{1,3,4}, Qing Kay Li, M.D., Ph.D.⁵, Richard B.S. Roden, Ph.D.¹, Marisa R. Nucci, M.D.⁶, Liang Cheng, M.D.⁷, Christopher G. Przybycin, M.D.⁸, Niloofar Nasser-Nik, M.D.⁹, Lee-Shu-Fune Wu, M.H.S.¹⁰, George J. Netto, M.D.¹¹, Brigitte M. Ronnett, M.D.^{1,3}, and Russell Vang, M.D.^{1,3}

¹Department of Pathology Division of Gynecologic, The Johns Hopkins University School of Medicine and Hospital, Baltimore, MD

²PhenoPath Laboratories, Seattle, WA

³Department of Gynecology & Obstetrics, The Johns Hopkins University School of Medicine and Hospital, Baltimore, MD

⁴Department of Oncology, The Johns Hopkins University School of Medicine and Hospital, Baltimore, MD

⁵Department of Pathology, The Johns Hopkins Bayview Hospital, Baltimore, MD

⁶Department of Pathology (Division of Women's and Perinatal Pathology), Brigham and Women's Hospital, Boston, MA

⁷Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN

⁸Robert J. Tomsich Pathology and Laboratory Medicine Institute, The Cleveland Clinic, Cleveland, OH

⁹Department of Pathology, South Miami Hospital, Baptist Health, South Miami, FL

¹⁰Department of International Health, Bloomberg School of Public Health, The Johns Hopkins University School of Medicine, Baltimore, MD

¹¹Divisions of Urologic Pathology, The Johns Hopkins University School of Medicine and Hospital, Baltimore, MD

Abstract

Immunohistochemical expression of GATA-3 is seen predominantly in non-neoplastic bladder and breast epithelium and their respective carcinomas; however, data on expression in normal and lesional trophoblastic tissues are limited. Immunohistochemical staining for GATA-3 was

Correspondence: Dr. Russell Vang, Department of Pathology (Division of Gynecologic Pathology), The Johns Hopkins Hospital, 401 North Broadway, Weinberg Building, Room 2242 Baltimore, MD 2123; Phone: (410) 502-0532; rvang1@jhmi.edu.

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assessed in a range of normal/lesional trophoblastic tissues and tumors in the differential diagnosis (n=445), including non-molar products of conceptions/2nd and 3rd trimester placentas/ ectopic pregnancies, hydatidiform moles, placental site nodules, normal/exaggerated implantation sites, choriocarcinomas, epithelioid trophoblastic tumors, placental site trophoblastic tumors, atypical smooth muscle tumors (including leiomyosarcoma), and cervical and pulmonary squamous cell carcinomas. The extent of expression (0 to 4+) and intensity (weak to strong) were recorded. All cases with developing trophoblast/non-neoplastic trophoblastic proliferations and 81% of trophoblastic neoplasms were positive. Of all non-neoplastic trophoblast cell types, expression was observed in cytotrophoblast in 89% of cases, syncytiotrophoblast in 50%, intermediate trophoblast in 100%, and villous trophoblastic columns in 100%. Increasing gestational age was associated with a decrease in extent/intensity of expression in non-neoplastic cytotrophoblast and syncytiotrophoblast while intermediate trophoblast maintained diffuse and strong expression from early to late gestation (p<0.0001). Eighty-nine percent of normal/exaggerated implantation sites showed 3+ or 4+ expression while staining in 55% of placental site nodules was 1+ or 2+. Staining for GATA-3 was present in 78% of choriocarcinomas, 95% of epithelioid trophoblastic tumors, and 71% of placental site trophoblastic tumors. While the number of choriocarcinomas and placental site trophoblastic tumors that showed a spectrum of expression ranging from negative to diffuse was relatively evenly distributed, 81% of epithelioid trophoblastic tumors had 3+ or 4+ staining. None of the atypical smooth muscle tumors and 3% of squamous cell carcinomas were positive, all of which exhibited weak staining. We conclude that GATA-3 is frequently expressed in normal and lesional trophoblastic tissues. It is also differentially expressed in intermediate trophoblast and cytotrophoblast/syncytiotrophoblast, which varies according to time during pregnancy. This study expands the spectrum of neoplasms known to express GATA-3. Thus, recognition of expression in trophoblastic tumors is important because it can present a diagnostic pitfall in the assessment of suspected metastatic bladder or breast carcinomas involving the gynecologic tract. In the evaluation of diagnostically problematic tumors for which trophoblastic neoplasms are in the differential diagnosis, such as leiomyosarcoma and squamous cell carcinoma, GATA-3 can be included as part of an immunohistochemical panel particularly when other trophoblastic markers are either not available or yield ambiguous results.

Keywords

GATA-3; trophoblast; choriocarcinoma; leiomyosarcoma; squamous cell carcinoma

INTRODUCTION

GATA-3 is an important transcription factor involved in embryogenesis¹. It is also a diagnostically useful immunohistochemical marker which is sensitive and relatively specific for bladder and breast non-neoplastic tissues and carcinomas. In urothelial carcinomas, expression has been observed in 67%-86% of cases²⁻⁴, and 48%-94% of breast carcinomas have been positive with a decrease noted with higher grade tumors.^{2, 4, 5-8} However, expression has also been occasionally observed in a variety of other tumors, including cutaneous squamous cell carcinoma, basal cell carcinoma, malignant mesothelioma, benign Brenner tumor, paraganglioma, pancreatic adenocarcinoma, and various types of salivary gland tumors.^{1,4,9} Although a number of series evaluating this marker in a spectrum of

different tumors have not assessed expression in non-neoplastic trophoblastic tissues and trophoblastic neoplasms,¹⁻² one recent large study by Miettinen *et al* included a small number of trophoblastic tissues/tumors and demonstrated that they frequently express GATA-3 (with positivity noted in trophoblastic cells of a developing embryo, pure choriocarcinomas, choriocarcinomatous components of mixed germ cell tumors, a placental site trophoblastic tumor, and syncytiotrophoblastic cells in seminomas).⁴ Nonetheless, all data in the literature on GATA-3 expression in trophoblastic tissues/neoplasms are relatively limited.

Prior to the publication of the study by Miettinen *et al*,⁴ we have encountered anecdotal GATA-3(+) trophoblastic lesions where the differential diagnosis included metastatic breast carcinoma, which created diagnostic confusion. Thus, expression of GATA-3 in trophoblastic lesions may be important to recognize as it has the potential to result in misclassification of a tumor in the gynecologic tract as metastatic bladder or breast carcinoma in morphologically ambiguous cases. Conversely, as GATA-3 may be frequently expressed in trophoblastic tumors, it could be an additional diagnostically helpful marker to include as part of an immunohistochemical panel for the evaluation of other lesions in the differential diagnosis. Therefore, the goals of this study were to assess immunohistochemical staining for GATA-3 in a large series of normal trophoblastic tissues, non-neoplastic trophoblastic proliferations, and trophoblastic neoplasms and compare expression in other tumors that can histologically simulate trophoblastic tumors, such as smooth muscle neoplasms and squamous cell carcinoma.

MATERIALS AND METHODS

Case selection

Normal trophoblastic tissues, non-neoplastic trophoblastic proliferations, trophoblastic neoplasms, and non-trophoblastic tumors were selected from the in-house and consultation files of our institutions. Four hundred forty-five cases were subjected to immunohistochemical analysis (244 cases analyzed by whole tissue sections, 201 by tissue microarrays), which included non-molar conceptions/placentas (n=77), hydatidiform moles (n=29), normal/exaggerated implantation sites (n=37), placental site nodules (n=20), choriocarcinomas (n=80), epithelioid trophoblastic tumors (n=21), placental site trophoblastic tumors (n=7), squamous cell carcinomas (n=136), and gynecologic atypical smooth muscle neoplasms (n=38).

The 77 non-molar cases consisted of 23 histologically unremarkable products of conception specimens/placentas, 19 ectopic pregnancies, 9 with known trisomies, and 26 with abnormal villous morphology (confirmed as biparental diploid by molecular genotyping). The 29 hydatidiform moles included 21 partial and 8 complete moles. Of the non-molar conceptions/placentas and hydatidiform moles, 54 were obtained from the 1st trimester, 18 the 2nd trimester, and 18 the 3rd trimester (in 16 cases, the gestational age was unknown).

Sixty-five of the 80 choriocarcinomas were from women and of gestational type, 1 was from a mixed choriocarcinoma and high-grade endometrial adenocarcinoma, and 14 were from men as part of a mixed germ cell tumor of the testicle. Thirty-three of the 38 atypical smooth

muscle tumors were leiomyosarcomas (29 usual/spindle cell type, 3 myxoid, 1 epithelioid) and 5 were smooth muscle tumors of uncertain malignant potential (STUMP). Forty and 96 squamous cell carcinomas were of cervical and pulmonary origin, respectively. Of the 201 cases assessed by tissue microarray (average of 3 cores per case; average diameter of 1 mm per core), all were from tumors (56 choriocarcinomas, 18 epithelioid trophoblastic tumors, 6 placental site trophoblastic tumors, 96 squamous cell carcinomas of lung, and 25 squamous cell carcinomas of cervix).

Immunohistochemical analysis

Immunohistochemical stains were performed at PhenoPath Laboratories using formalin-fixed, paraffin-embedded tissue sections. Unstained sections were deparaffinized and rehydrated before performing antigen retrieval (8 minutes in a pressure cooker at 95° C with 0.01M citrate buffer, pH 6.0). Following pre-treatment, anti-GATA-3 mouse monoclonal antibody (1:6000, clone L50-823; Biocare Medical, Concord, CA) was applied to respective sections and incubated for 30 minutes at room temperature. Antibody localization was achieved using the Ultravision Quanto detection system (Thermo Scientific; Waltham, MA) using a Dako Autostainer (Dako; Carpinteria, CA). The slides were then incubated in 3,3'-diaminobenzidine (DAB+; Dako, Carpinteria, CA).

Tissues were considered positive only if nuclear expression within trophoblastic cells was present (or in the case of non-trophoblastic neoplasms, nuclear expression within tumor cells). The immunostaining was interpreted by two pathologists (NB and RV), with assessment of both staining distribution (0, <5% positive cells; 1+, 5%-24%; 2+, 25%-49%; 3+, 50%-74%; 4+, 75%-100%) and intensity (1, weak; 2, moderate; 3, strong). These values were converted into immunohistochemical composite scores by multiplying the individual scores of distribution by intensity (possible range of values from 0 to 12). For example, a case with 3+ distribution (3 points) and moderate intensity (2 points) would have an immunohistochemical composite score of $3 \times 2 = 6$. For reporting the overall frequency of staining, cases with at least 1+ extent of expression were considered positive, and cases with staining in <5% of trophoblastic/tumor cells were negative.

In non-neoplastic cases, GATA-3 staining was scored separately in all of the different types of trophoblastic cells, including cytotrophoblast, syncytiotrophoblast, implantation-type intermediate trophoblast, chorionic-type intermediate trophoblast (including assessment of fetal membranes and placental site nodules), intermediate trophoblastic islands, and villous trophoblastic columns. As the distinction between normal and exaggerated implantation sites is subjective, both were combined for purposes of immunohistochemical analysis. Gestational age was correlated with immunohistochemical expression in non-neoplastic cases for which the gestational age was known.

Statistical analysis

For non-neoplastic cases, differences in the mean immunohistochemical composite scores between the various types of trophoblast were analyzed by the ANOVA test. Correlation coefficients of immunohistochemical expression for each trimester of pregnancy were

calculated by multiple linear regression analysis. The significance level was set at <0.05 . All analyses were done using SAS version 9.3 statistical software (SAS, Inc.; Cary, NC).

RESULTS

Developing/non-neoplastic trophoblast (including non-molar conceptions/placentas/ectopic pregnancies, hydatidiform moles, normal/exaggerated implantation sites, and placental site nodules)

The frequency of positive staining and extent/intensity of expression for each category of tissue/lesion are listed in Tables 1 and 2, respectively (Fig. 1). Among all non-neoplastic cases, GATA-3 was expressed in cytotrophoblast in 89% of cases with a patchy pattern of expression (mean extent score, 2.5) and mild-moderate intensity (mean intensity score, 1.9). Villous stroma of non-molar and molar cases was negative. Fifty percent of cases exhibited expression in syncytiotrophoblast, usually with limited extent of staining and weak expression (mean extent and intensity scores, 1.1 and 1.1, respectively). GATA-3 was expressed in all types of intermediate trophoblast (Figs. 1F, 1H, and 2) in 100% of cases, typically with diffuse staining (range of mean extent scores for each type of intermediate trophoblast, 3.1–3.8) and strong intensity (range of mean intensity scores for each type of intermediate trophoblast, 2.6–2.9). In particular, expression within fetal membranes was confined to the chorion layer (Fig. 1 H) with only occasional focal weak staining in the amnionic epithelium, and the stroma was negative. The villous trophoblastic columns (Figs. 1B and D) in all cases were positive for GATA-3, usually with diffuse staining (mean extent score, 3.9) and strong intensity (mean intensity score, 3.0). However, no particular gradient pattern or polarization of staining was apparent within the columns.

In non-molar conceptions/placentas and hydatidiform moles, staining in cytotrophoblast, syncytiotrophoblast, and intermediate trophoblast was assessed with respect to gestational age to determine expression patterns as a function of time (sufficient numbers of cases with villous trophoblastic columns were not available for analysis in the 2nd or 3rd trimesters). As the general staining characteristics of all the types of intermediate trophoblast were relatively similar, they were combined into a single category of intermediate trophoblast for study purposes (Table 3). Also, as the staining characteristics of non-molar cases (products of conception specimens, vaginal deliveries/cesarean sections, trisomies, and ectopic pregnancies) and hydatidiform moles (both partial and complete) were similar within each trimester, they were all analyzed together. The mean immunohistochemical composite scores for cytotrophoblast and syncytiotrophoblast decreased from the 1st through 3rd trimesters (cytotrophoblast, 9.0 to 1.6; syncytiotrophoblast, 5.9 to 0.1). In contrast, the intermediate trophoblast maintained robust expression throughout pregnancy (11.3 to 11.8). This difference in patterns of expression in intermediate trophoblast versus cytotrophoblast/syncytiotrophoblast was statistically significant ($p<0.0001$).

In normal/exaggerated implantation sites and placental site nodules (Figure 2), details regarding the extent and intensity of staining are listed in Table 2. All normal/exaggerated implantation sites and placental site nodules were positive, and both lesions typically exhibited moderate intensity of staining. However, 89% of normal/exaggerated implantation

sites showed 3+ or 4+ expression while staining in 55% of placental site nodules was 1+ or 2+.

Trophoblastic neoplasms

GATA-3 was expressed in 78%, 95%, and 71% of choriocarcinomas, epithelioid trophoblastic tumors, and placental site trophoblastic tumors, respectively. Details of extent and intensity are listed in Table 2. While the number of choriocarcinomas (Figs. 3A and B) and placental site trophoblastic tumors that showed a spectrum of expression ranging from 0 to 4+ was relatively evenly distributed, 81% of epithelioid trophoblastic tumors (Figs. 3C and D) had 3+ or 4+ expression. The intensity of staining in choriocarcinoma and placental site trophoblastic tumor/epithelioid trophoblastic tumor was usually weak and moderate, respectively. In choriocarcinomas, the mononuclear component showed a greater extent and intensity of staining than the syncytiotrophoblastic component in the vast majority of cases (Fig. 3B). Of the 14 choriocarcinomas in males, 4 had a non-choriocarcinoma germ cell component. Two had teratomatous elements, which were negative for GATA-3. The other 2 had a component of yolk sac tumor. Among the latter, 1 was negative for GATA-3 while focal (1+) expression with weak intensity was seen in the other. Of note, the trophoblastic tumors generally had slightly lesser extents and intensities of staining compared with non-neoplastic cases.

Non-trophoblastic neoplasms

Of the 96 squamous cell carcinomas of the lung, only one (1%) case showed positivity for GATA-3 (4+ extent, weak). Only 3 (8%) of the 40 squamous cell carcinomas of the cervix were positive, all with weak intensity. Two of these exhibited 1+ extent of expression while the remaining case was 2+. All 38 atypical smooth muscle neoplasms were negative.

Background normal tissue

Most background tissues were noted to be typically negative, including myometrium, endometrial glands and stroma/decidua, fetal parts (including cartilage, neural tissue, skeletal muscle, bowel, and heart), blood vessels, fallopian tube mucosa and myosalpinx, endocervical glands, cervical stroma, lung, and colonic mucosa. Occasionally, scattered weak-moderate staining was noted in background inflammation, and rarely background benign cervical squamous epithelium was focally weakly positive.

DISCUSSION

In our study, GATA-3 was expressed in most developing trophoblast/non-neoplastic trophoblastic proliferations and trophoblastic neoplasms. In normal trophoblast, non-neoplastic trophoblastic proliferations, and trophoblastic neoplasms, GATA-3 was positive in all trophoblast cell types. However, staining (extent and intensity) was greatest in intermediate trophoblast and least in syncytiotrophoblast. Of note, the 2 main types of intermediate trophoblast (implantation- and chorionic-types), including their non-neoplastic and neoplastic counterparts, expressed GATA-3. These data show that GATA-3 is a sensitive marker for trophoblastic tumors and expand the spectrum of tissues/tumors known to express this marker.

Neoplasms that frequently express GATA-3, such as breast or bladder carcinomas, may occasionally involve the gynecologic tract, including the cervix, endometrium, or myometrium. It is these specific sites where differential diagnostic problems may occur since trophoblastic tumors primarily arise in the uterine cervix and/or corpus; moreover, trophoblastic tumors can rarely develop primarily in the ovaries and fallopian tubes, which are also potential sites involved by metastatic breast or bladder carcinoma. In this context and if immunohistochemistry is needed for a poorly differentiated or non-specific appearing tumor without classic histologic features, immunostaining for GATA-3 will not differentiate these tumors. Thus, failure to recognize that trophoblastic neoplasms can express GATA-3 may result in tumor misclassification. Accordingly, distinction of these tumors from a trophoblastic neoplasm will have to be based on a combination of clinical history (prior breast/bladder carcinoma or complete hydatidiform mole), laboratory data (serum β -hCG), focal morphologic features suggestive of either breast/bladder carcinoma or a trophoblastic neoplasm, and/or other immunohistochemical stains. A useful panel of immunostains can include ER, PR, GCDFP-15, and other sensitive and relatively specific trophoblastic markers, such as CD146 (Mel-CAM),^{10–12} HLA-G,^{11–12} hydroxyl-delta-5-steroid dehydrogenase (HSD3B1),^{13–15} and β -hCG.

In contrast with breast and bladder carcinomas, immunostaining for GATA-3 can be useful for other tumors in the differential diagnosis of trophoblastic neoplasms, such as smooth muscle tumors and squamous cell carcinoma, especially if immunostaining for other markers is unhelpful. In particular, placental site trophoblastic tumor can histologically simulate uterine leiomyosarcoma. GATA-3 was negative in all 36 gynecologic atypical smooth muscle tumors (including leiomyosarcoma) in this study. Expression in uterine leiomyosarcomas has not been thoroughly assessed in the literature, but 2 studies including cases of non-gynecologic type have been published, both of which show that leiomyosarcomas are only infrequently positive.^{4,16}

Also, epithelioid trophoblastic tumor can arise in the cervix or metastasize to the lungs and, therefore, histologically simulate cervical or pulmonary squamous cell carcinoma, respectively. In our study, GATA-3 was positive in only 3% of 136 squamous cell carcinomas of cervical or pulmonary origin. The positive cases exhibited variable extent of staining although the majority were focal-patchy, and all had weak intensity. In the context of the available data in the literature^{2–4, 17–20}, our results show that for squamous cell carcinomas that would typically be considered in the differential diagnosis of epithelioid trophoblastic tumor (cervix and lung), GATA-3 is expressed in only a subset of cases, often with limited extent and sometimes weak intensity. Therefore, in combination with other immunohistochemical stains (including p16,^{21–22} actins, desmin, cytokeratins, and/or other trophoblast-specific markers), GATA-3 can be a useful and discriminatory marker when smooth muscle tumors or squamous cell carcinomas are in the differential diagnosis of a trophoblastic neoplasm. However, it should be noted that some markers frequently positive in squamous cell carcinomas, such as p63 and p40, may be expressed in trophoblastic neoplasms. In particular, diffuse strong expression of p63 is typical of epithelioid trophoblastic tumor. In addition, although trophoblastic tumors would be expected to be negative for smooth muscle markers, we are unaware of any rigorous evaluation for those markers in trophoblastic neoplasms in the literature.

In general, when selecting immunohistochemical markers to be used as part of a panel to evaluate a potential trophoblastic neoplasm, it is worth noting that antibodies for trophoblastic-specific markers, such as CD146, HLA-G, and HSD3B1, are commercially available although not all pathology laboratories have them. On the other hand, many pathology laboratories frequently carry the anti-GATA-3 antibody. It should also be noted that other limitations exist for these markers or other traditional trophoblastic markers, which may further make GATA-3 a useful immunostain. Occasional expression of CD146 and HLA-G has been noted in carcinomas,²³ other traditional trophoblastic markers such as hPL and inhibin have sensitivities or specificities that may not be ideal,²³ and carcinomas with choriocarcinomatous differentiation can express β -hCG. Hence, in cases where non-breast/non-bladder tumors enter the differential diagnosis and immunohistochemistry is needed, GATA-3 can be included as part of a panel with the aforementioned trophoblastic markers, especially if either technical or interpretational difficulties occur with CD146, HLA-G, and/or HSD3B1 or they are unavailable.

A finding of interest in this study is that choriocarcinomas in both women and men are positive for GATA-3 and that staining for GATA-3 in mixed germ cell tumors is essentially restricted to the choriocarcinoma component. Other investigators have also noted that the choriocarcinoma component of mixed germ cell tumors are positive for GATA-3, as well as that pure seminomas and embryonal carcinomas are negative, although results for expression in yolk sac tumor have varied.^{2,4} Hence, the utility of this marker is not restricted to just gynecologic choriocarcinomas. Moreover, as the choriocarcinomas in women in this study were mainly of gestational type and those from men were part of mixed germ cell tumors, these findings support the concept that GATA-3 is only a differentiation-specific trophoblastic marker in contrast to GATA-3 playing a differential role in a dualistic pathway of choriocarcinoma development (i.e., gestational versus germ cell pathways).

A novel observation for developing trophoblast in our study is that immunohistochemical expression of GATA-3 in cytotrophoblast/syncytiotrophoblast typically decreases during gestation while intermediate trophoblast maintain robust staining from the 1st through 3rd trimesters. A number of molecular studies of *GATA-3* in gestational tissues have been conducted. During pregnancy, *GATA-3* is thought to be a significant gene that directs trophoblast differentiation and regulates other important genes expressed in trophoblast/placenta, such as *GATA-2*, *CDX2*, placental lactogen, *HSD17B1*, and *ASCL2*.^{24–31} However, the specific role and mechanism of action of the *GATA-3* gene and protein in the developing placenta have not been definitively established. Nonetheless, in a study by Ng *et al*, it was demonstrated that *GATA-3* mRNA levels in mouse trophoblast are highest in mid-gestation with a decrease later in pregnancy.³² *GATA-3* mRNA was produced in placental “trophoblast giant cells” in that study, but it is unclear whether they were actually syncytiotrophoblast or multinucleated intermediate trophoblast- an important point as expression was notably low in syncytiotrophoblast in our study. These combined immunohistochemical and molecular findings suggest differential expression of the *GATA-3* gene in intermediate trophoblast and cytotrophoblast/syncytiotrophoblast, which may vary according to time during pregnancy. Further molecular studies to elucidate the exact

biologic functions of this gene in the different types of developing trophoblast in humans, however, are warranted.

In conclusion, normal trophoblastic tissues, non-neoplastic trophoblastic proliferations, and trophoblastic tumors show immunohistochemical expression of GATA-3, and differential GATA-3 expression may occur in the different types of trophoblastic cells during normal development. These findings expand the spectrum of tissues/tumors known to express this marker. Hence, failure to recognize that trophoblastic neoplasms can express GATA-3 may present a diagnostic pitfall during the immunohistochemical evaluation of a tumor with clinical or histologic suspicion for a breast or bladder carcinoma involving the gynecologic tract. In the context of tumors that are frequently GATA-3(–) such as smooth muscle tumors or cervical/pulmonary squamous cell carcinoma, GATA-3 can be a helpful immunohistochemical marker for diagnosing trophoblastic tumors when included as part of a panel of antibodies, and it can also serve as an alternative trophoblastic marker when other specific trophoblastic markers either may not be available or yield ambiguous results.

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Figure 1.

Ectopic pregnancy, 1st trimester (A, H&E; B, GATA-3)- The cytotrophoblast and villous trophoblastic columns show diffuse strong expression. The syncytiotrophoblast are negative. Complete hydatidiform mole, 1st trimester (C, H&E; D, GATA-3)- Diffuse strong staining is present within villous trophoblastic hyperplasia and villous trophoblastic columns. 2nd trimester placenta (E, H&E; F, GATA-3)- GATA-3 is diffusely expressed with moderate-strong intensity in the intermediate trophoblastic island, but staining in the cytotrophoblast is substantially decreased in extent and intensity. The syncytiotrophoblast are largely negative. Fetal membranes, 3rd trimester (G, H&E; H, GATA-3)- The chorionic-type intermediate trophoblast are diffusely positive with strong intensity while the amnionic epithelium is negative.

Figure 2.

Exaggerated implantation site (A, H&E; B, GATA-3)- Diffuse strong expression within implantation-type intermediate trophoblast. Multinucleated intermediate trophoblastic cells are also positive. Placental site nodule (C, H&E; D, GATA-3)- The chorionic-type intermediate trophoblastic cells show diffuse strong staining.

Figure 3.

Choriocarcinoma (A, H&E; B, GATA-3)- The monophasic component shows diffuse weak-moderate staining; however, the syncytiotrophoblastic component is mostly negative.

Epithelioid trophoblastic tumor (C, H&E; D, GATA-3)- GATA-3 is diffusely positive with moderate-strong intensity in the neoplastic chorionic-type intermediate trophoblastic cells.

Table 1

Frequency of GATA-3 expression

Lesion	n	Percent cases positive
<i>Non-molar conception/placenta</i>	77	100
<i>Hydatidiform mole</i>	29	100
<i>Normal/exaggerated implantation site</i>	37	100
<i>Placental site nodule</i>	20	100
<i>Choriocarcinoma</i>	80	78
<i>Epithelioid trophoblastic tumor</i>	21	95
<i>Placental site trophoblastic tumor</i>	7	71
<i>Squamous cell carcinoma</i>	136	3
<i>Atypical smooth muscle neoplasm</i>	38	0
Total	445	

Table 2

Extent and intensity scores for GATA-3 expression in normal trophoblastic tissues and trophoblastic non-neoplastic proliferations and tumors

Lesion	Extent					Mean Intensity
	0	1+	2+	3+	4+	
<i>Non-molar conceptions/placentas</i>	0	7	15	23	32	2.5
<i>Hydatidiform moles</i>	0	0	6	12	11	2.3
<i>Normal/exaggerated implantation site</i>	0	1	3	6	27	2.8
<i>Placental site nodule</i>	0	3	8	4	5	2.4
<i>Choriocarcinoma</i>	18	13	12	20	17	1.4
<i>Epithelioid trophoblastic tumor</i>	1	2	1	6	11	2.1
<i>Placental site trophoblastic tumor</i>	2	2	1	0	2	1.6

Table 3

Correlation of mean immunohistochemical composite scores with gestational age for developing/non-neoplastic trophoblast

Type of trophoblast	Trimester		
	1 st *	2 nd †	3 rd ¶
<i>Cytotrophoblast</i> [§]	9.0	3.7	1.6
<i>Syncytiotrophoblast</i> [‡]	5.9	2.6	0.1
<i>Intermediate trophoblast</i> ^{**}	11.3	10.7	11.8

* p<0.0001 for all 3 cell types within 1st trimester

† p<0.0001 for all 3 cell types within 2nd trimester

¶ p<0.0001 for all 3 cell types within 3rd trimester

§ p<0.0001 for all 3 trimesters within cytotrophoblast group

‡ p<0.0001 for all 3 trimesters within syncytiotrophoblast group

** p=0.327 for all 3 trimesters within intermediate trophoblast group