Usefulness of a Monoclonal ERG/FLI1 Antibody for Immunohistochemical Discrimination of Ewing Family Tumors

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Abstract

Ewing family tumors (EFTs) and prostate carcinomas are characterized by rearrangement of ETS genes, most commonly FLI1 (EFTs) and ERG (prostate carcinomas). Previously, we characterized an antibody against ERG (EPR3864) for detecting ERG-rearranged prostate carcinoma. Because EPR3864 also cross-reacts with FLI1, we evaluated the usefulness of EPR3864 for discriminating EFTs from other small round blue cell tumors (SRBCTs) with immunohistochemistry. Of 57 evaluable EFTs, 47 (82%) demonstrated at least moderate, diffuse, nuclear ERG/FLI1 staining (including 89% and 100% of cases with confirmed EWSR1:FLI1 and EWSR1:ERG fusions, respectively), of which 1, 3, and 43 showed negative, cytoplasmic, or membranous CD99 staining, respectively. Among other SRBCTs (61 cases, 7 types), at least moderate, diffuse, nuclear EPR3864 staining was seen in all precursor B-lymphoblastic lymphomas/leukemias and subsets of Burkitt lymphomas (10%) and synovial sarcomas (45%). In summary, EPR3864 may be useful in detecting EWSR1:FLI1 and EWSR1:ERG rearranged EFTs in addition to prostate carcinomas.

Ewing family tumors (EFTs), which encompass Ewing sarcomas/peripheral neuroectodermal tumors, are characterized by chromosomal rearrangements fusing EWSR1 to members of the ETS transcription factor family. Although most commonly fused to the ETS gene FLI1 (~90%) through t(11;22)(q24;q12), EWSR1 can also fuse to ERG (~5%-10%) and rarely to ETV1, FEV, ETV4, and ETV5.1,4 EFTs and other small round blue cell tumors (SRBCTs), including neuroblastomas, rhabdomyosarcomas, synovial sarcomas (poorly differentiated and monophasic variants), lymphoblastic lymphomas/leukemias, desmoplastic small round cell tumors, and nephroblastomas (Wilms tumor) can be morphologically indistinguishable. Definitive diagnosis commonly involves immunohistochemistry, typically against CD99 and FLI1, and molecular tests.2,5-15

CD99, also known as MIC2, encodes an integral membrane glycoprotein and shows diffuse membranous staining in more than 90% of EFTs with immunohistochemistry using various monoclonal antibodies (including 12E7, HBA71, and O13).12,14,15 In addition, less specific cytoplasmic staining can also be observed. However, CD99 is not specific for EFTs because it also stains lymphoblastic lymphomas/leukemias,16 anaplastic large cell lymphomas,20 synovial sarcomas,21 synovial sarcomas,22,23 and some rhabdomyosarcomas,24 as well as various other tumors.16-20

The EWSR1:FLI1 gene fusion results in the fusion of the N-terminus of EWSR1 to the C-terminus of FLI1, which preserves the ETS DNA-binding domain, and transforms NIH 3T3 cells.21,22 FLI1 is normally expressed in endothelial and hematopoietic cells,5 and consistent with its role as a transcription factor, both FLI1 and the EWSR1:FLI1 product show nuclear localization.5,33 Both polyclonal and
monoclonal antibodies against FLI1 have been shown to be diagnostically useful in EFTs, with staining of 63% to 89% (median, 81%)6,9,10,34-36 and 75% to 100% (median, 91%)7,9,37,38 of EFTs, respectively. In addition to EFTs, both monoclonal and polyclonal antibodies against FLI1 have been reported to also stain vascular tumors, lymphoblastic lymphomas, and Merkel cell carcinomas, as well as a fraction of other SRBCTs, including poorly differentiated synovial sarcomas, and other non-Hodgkin lymphomas.3-7,9,20,35,37,39 Polyclonal antibodies against FLI1 have also been reported to stain at least some oligary neuroblastomas, desmoplastic small round cell tumors, and other carcinomas (but not prostate carcinomas).6,35 Similarly, monoclonal antibodies against FLI1 have been reported to stain hemangiopericytomas, neuroendocrine carcinomas, melanomas, lung adenocarcinoma, and various normal tissues, including prostate, breast, and colon epithelium.7,9 In the only head-to-head comparison we are aware of, Mhawech-Fauceglia et al9 reported that monoclonal antibodies against FLI1 were more sensitive for EFTs, whereas polyclonal antibodies were more specific, consistent with other published studies.

Like EFTs, prostate carcinoma is characterized by chromosomal rearrangements involving ETS transcription factor family members, which are fused to the 5′ untranslated regions of androgen-regulated genes and occur in approximately half of all prostate carcinomas.40-42 Fusions involving ERG (most commonly TMPRSS2:ERG) represent approximately 90% of all ETS fusions in prostate carcinoma, with less frequent fusions involving ETV1, ETV4, ETV3 and 1 reported case involving FLI1.40-44 Recently we and others demonstrated the usefulness of a novel rabbit monoclonal antibody raised against the C-terminus of ERG (clone EPR3864), which demonstrates high sensitivity and specificity (>95%) for the detection of ERG-rearranged prostate carcinoma.55-57 As Mohamed et al54 recently demonstrated, EPR3864 also reacts with exogenous FLI1 on Western blotting54; similarly, we hypothesized that EPR3864 may also be useful for distinguishing EFTs from other SRBCTs. Herein we characterize EPR3864 staining of ERG/FLI1 with immunohistochemistry in the discrimination of EFTs.

Table I

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. (% of Patients)</th>
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<tbody>
<tr>
<td>Age at diagnosis, y (n = 49)†</td>
<td>18 (13-30)</td>
</tr>
<tr>
<td>Median age (IQR), y</td>
<td>18 (13-30)</td>
</tr>
<tr>
<td>Sex (n = 49)</td>
<td>Male 29 (59)</td>
</tr>
<tr>
<td></td>
<td>Female 20 (41)</td>
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<tr>
<td>Stage (n = 57)ップ</td>
<td>Primary 37 (65)</td>
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<tr>
<td></td>
<td>Primary; status post chemotherapy 4 (7)</td>
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<tr>
<td></td>
<td>Recurrence 6 (11)</td>
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<tr>
<td></td>
<td>Metastasis 10 (18)</td>
</tr>
<tr>
<td>Location (n = 57)ップ</td>
<td>Osseous; axial 18 (32)</td>
</tr>
<tr>
<td></td>
<td>Osseous; extra-axial 19 (32)</td>
</tr>
<tr>
<td></td>
<td>Extraosseous; axial 18 (32)</td>
</tr>
<tr>
<td></td>
<td>Extraosseous; extra-axial 2 (4)</td>
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<tr>
<td>Molecular confirmation (n = 49) לך</td>
<td>EWSR1:FLI1 29 (59)</td>
</tr>
<tr>
<td></td>
<td>EWSR1:ERG 3 (6)</td>
</tr>
<tr>
<td></td>
<td>No EWSR1 rearrangement 6 (12)</td>
</tr>
<tr>
<td></td>
<td>NA 11 (22)</td>
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</tbody>
</table>

EFT, Ewing family tumor; IQR, interquartile range; NA, not available.

† Total number of patients with at least 1 evaluable core used for age at diagnosis and sex.
 pepp Total number of cases with at least 1 evaluable core used for stage and location.
 YORK Patients who had at least 1 case confirmed by 2 of 3 molecular tests (fluorescence in situ hybridization for EWSR1 breakapart, cytogenetics [(t11;22) or t21;22]) and reverse transcriptase-polymerase chain reaction for EWSR1:FLI1 or EWSR1:ERG).

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RT-PCR) were concordant. All tissue samples were obtained with prior institutional review board approval.

Immunohistochemistry for ERG/FLI1 on the tissue microarray and single sections of EFTs and other SRBCTs was performed as described using a ready-to-use, prediluted monoclonal antibody against ERG, clone EPR3864 (Ventana Medical Systems, Tucson, AZ). Staining of vessels was used as a positive control, and cores or sections without staining of vessels were excluded from further analysis. Nuclear ERG/FLI1 staining intensity was scored as 0 (absent), 1+ (weak), 2+ (moderate), or 3+ (strong). Unless otherwise indicated, staining was diffuse (>80% of tumor). Immunohistochemistry for CD99 was performed on the tissue microarray using the rabbit monoclonal antibody EPR3097 (BioCare Medical, Concord, CA) at a 1:200 dilution for 30 minutes with Envision+ horseradish peroxidase detection (Dako, Carpinteria, CA). Epitope retrieval was performed using 10 μmol/L of citrate buffer (pH 6) in a microwave for 10 minutes. Immunohistochemistry for CD99 was performed previously on the single sections of EFTs during the diagnostic workup and was re-reviewed. Staining for CD99 was scored as negative, cytoplasmic, or membranous. Unless otherwise indicated, staining was diffuse. EFT presence and viability and ERG/FLI1 and CD99 staining were evaluated by S.A.T, J.N.S., and L.P.K., with discrepancies resolved by D.R.L.

Analysis

EFT cases in which no viable tumor was present in any of the 3 cores were excluded from further analysis. In cases with variable expression in 2 or more cores, the greatest staining in any core was reported as the overall score and variable expression was noted. Association between ERG/FLI1 and CD99 staining was evaluated with the 2-tailed Fisher exact test using GraphPad Prism version 5 (GraphPad Software, San Diego, CA).

Results

Fifty-five EFT cases from 47 patients had at least 1 core with viable tumor and were evaluable for FLI1/ERG and CD99 staining (from a tissue microarray with 105 cases from 85 patients). Single formalin-fixed paraffin-embedded sections from 2 additional EFTs (from patients not represented on the tissue microarray) were evaluable for ERG/FLI1 staining as well as CD99 staining performed at diagnosis. Thus, our final evaluable cohort consisted of 57 EFT cases from 49 patients, as summarized in Table 1. ERG/FLI1 staining was scored as strong (3+), moderate (2+), weak (1+), or negative (0), whereas CD99 staining was scored as membranous or cytoplasmic (both positive) or negative. Examples of ERG/FLI1 and CD99 staining are shown in Image 1. Among control cores of normal tissue on the tissue microarray, normal spleen and tonsil showed 3+ ERG/FLI1 staining, whereas normal ovary, lung, spinal cord, colon, kidney, liver, and testes were negative (0+).

Of the 55 evaluable cases on the tissue microarray, 54 (98%) showed homogeneous ERG/FLI1 staining between evaluable cores, and thus all cases were scored based on the highest staining intensity. The primary case from patient 8 showed 2 cores with 3+ ERG/FLI1 staining and 1 core with 1+ staining; a metastatic lesion from this patient showed 3 cores with 3+ ERG/FLI1 staining. Of the 6 additional patients with more than 1 evaluable case on the tissue microarray, 2 showed different ERG/FLI1 staining intensity between cases. Patient 3 had 3 evaluable metastatic cases, with 2 showing 3+ ERG/FLI1 staining in each of the 3 cores and 1 showing 2+ ERG/FLI1 staining in all 3 cores. The primary case from patient 28 showed negative ERG/FLI1 staining in all 3 cores, and a recurrence showed 2+ staining in all 3 cores. All evaluable cases on the tissue microarray showed homogeneous CD99 staining in evaluable cores, and 1 patient had 2 cases with discordant CD99 staining. Patient 6 had 1 case (a lung metastasis) showing membranous CD99 expression in 1 evaluable core, whereas a separate case (a femur metastasis) showed negative CD99 staining (Image 2).

Of the 57 evaluable EFT cases, 6 (11%) demonstrated negative (0) ERG/FLI1 staining, 4 (7%) demonstrated weak (1+) staining, 13 (23%) demonstrated moderate (2+) staining, and 34 (60%) demonstrated strong (3+) staining (Image 2). All EFTs with positive ERG/FLI1 staining showed diffuse nuclear ERG/FLI1 expression. Of the 47 (82%) EFTs with at least moderate (2+) ERG/FLI1 staining, 1 (2%) showed negative CD99 staining, 3 (6%) showed cytoplasmic staining, and 43 (91%) showed membranous staining. Of the remaining 10 (18%) EFTs with negative to weak (0 to 1+) ERG/FLI1 staining, 3 (30%) showed negative CD99 staining, 2 (20%) showed cytoplasmic staining, and 5 (50%) showed membranous staining (Image 2). Overall, at least moderate (2+) ERG/FLI1 staining and membranous CD99 staining were significantly associated (43 of 57 evaluable cases, \( P = .005 \), Fisher exact test), and 52 (91%) of 57 of cases showed either at least moderate (2+) ERG/FLI1 staining or membranous CD99 staining.

Of the 57 cases, 45 (79%) had evaluable molecular data. Of evaluable cases, 35 (78%) harbored EWSR1:FLI1 fusions, 4 (9%) harbored EWSR1:ERG fusions, and 6 (13%) lacked evidence of EWSR1 rearrangements. Among the 35 cases with EWSR1:FLI1 fusions, 31 (89%) showed at least moderate ERG/FLI1 staining, and 30 (86%) showed membranous CD99 staining. All 4 cases with EWSR1:ERG fusions showed at least moderate ERG/FLI1 staining and membranous CD99 staining. Lastly, among the 6 cases without evidence of EWSR1 rearrangement, 2 (33%) showed at least moderate ERG/FLI1 staining and 4 (67%) showed membranous CD99 staining. Importantly, these results confirm the ability...
of EPR3864 to detect the products of both \textit{EWSR1:FLI1} and \textit{EWSR1:ERG} gene fusions.

In addition to EFTs, we also evaluated ERG/FLI1 staining using single sections from 61 other SRBCTs \textit{Image 3}. Among other SRBCTs, at least 2+ focal nuclear staining was observed in 0 of 11 nephroblastomas (Wilms tumors), 0 of 11 neuroblastomas, 0 of 7 alveolar/embryonal rhabdomyosarcomas, 0 of 4 desmoplastic small round cell tumors, 4 (40\%) of 10 Burkitt lymphomas, 9 (82\%) of 11 synovial sarcomas (10 monophasic, 1 poorly differentiated), and 7 of 7 precursor B-lymphoblastic lymphomas/leukemias. Of all non-EFTs stained for ERG/FLI1, at least 2+ diffuse nuclear staining was seen in 1 (10\%) of 10 Burkitt lymphomas, 5 (45\%) of 11 synovial sarcomas, and 7 of 7 of precursor B-lymphoblastic lymphomas/leukemias. A heat map of ERG/FLI1 staining in all SRBCTs is shown in Image 3.

\textbf{Discussion}

The distinction of EFTs from other SRBCTs often requires immunohistochemistry in addition to morphology, cytogenetics, and/or molecular techniques. CD99 shows...
high sensitivity for EFTs, but it is not entirely specific. A combination of CD99, FLI1, HNK1, and CAV1 shows high specificity and sensitivity for EFTs and has been proposed as an immunohistochemistry panel for the differential diagnosis of SRBCTs. Both polyclonal and monoclonal antibodies against FLI1 have been used, each with described limitations.

Previously we identified EPR3864, a monoclonal antibody against ERG, as being useful for detecting gene fusions involving ERG in prostate cancer (most commonly TMPRSS2:ERG), which occur in approximately half of all prostate cancers identified by prostate-specific antigen screening. More recently, Mohamed et al showed that EPR3864 also detects FLI1, but another recently developed monoclonal antibody against ERG does not react with FLI1 and stains only 7% of EFTs. FLI1 cross-reactivity of EPR3864 does not appear to be relevant in prostate cancer, given the more

**Image 2** ERG/FLI1 and CD99 staining in Ewing family tumors (EFTs). A. Heat map of molecular status and ERG/FLI1 and CD99 staining for 57 evaluable EFT cases. Cases with confirmed EWSR1:FLI1 (black) or EWSR1:ERG (purple) rearrangements are indicated, along with cases without evidence of an EWSR1 rearrangement (white) or those not assessed (gray). ERG/FLI1 staining (diffuse nuclear) and CD99 staining were scored as in Image 1. Cases shown in Image 1 are indicated in yellow. B, D. Representative H&E (left panels), ERG/FLI1 (middle panels), and CD99 (right panels) cores from cases showing 3+ ERG/FLI1 expression and cytoplasmic (Cyto) (B, C) or negative (Neg) (D) CD99 staining are shown. Cases shown are indicated in white in A (magnification, ×10; inset, ×20).
than 95% sensitivity and specificity of EPR3864 for detecting ERG-rearranged prostate cancer and the more than 99.99% reported specificity for cancer. However, we hypothesized that this antibody may be useful for differentiating EFTs that harbor both FLI1 and ERG rearrangements.

Based on immunohistochemical examination with EPR3864, we found that 82% (47/57) of EFTs (including 89% of cases with confirmed EWSR1:FLI1 fusions and 100% of cases with confirmed EWSR1:ERG fusions) show at least moderate nuclear staining of ERG/FLI1, which was always diffuse. This rate is comparable to those reported using other polyclonal and monoclonal antibodies against FLI1. In addition, at least moderate ERG/FLI1 staining and membranous CD99 staining were significantly associated in our study, with 91% of cases showing either at least moderate ERG/FLI1 staining or membranous CD99 staining.

Among 61 other SRBCTs, no Wilms tumors, neuroblastomas, rhabdomyosarcomas, or desmoplastic small round cell tumors.

**Image 3** ERG/FLI1 staining in small round blue cell tumor (SRBCT) mimickers of Ewing family tumors (EFTs). **A**, Heat map of ERG/FLI1 staining (nuclear) in 61 non-EFT SRBCTs. ERG/FLI1 staining was scored as in Images 1 and 2. In cases with heterogeneous staining, the variable intensity is indicated by multiple colors in the heat map cell. Cases shown are indicated in yellow. **B-H**, H&E (top panels) and ERG/FLI1 (bottom panels) staining for representative cases are shown (×20). DSCRT, desmoplastic small round cell tumors.
round cell tumors showed at least focal moderate (2+) ERG/FLI1 staining. However, we observed at least focal, moderate ERG/FLI1 staining in 40% of Burkitt lymphomas, 82% of monophasic synovial sarcomas, and 100% of precursor B-lymphoblastic lymphomas. Unlike EFTs, which always showed diffuse ERG/FLI1, heterogeneous absent-weak (0 to 1+) or weak-moderate (1 to 2+) staining was observed in 25% of desmoplastic small round cell tumors, 9% of Wilms tumors, and 30% of Burkitt lymphomas, suggesting that only diffuse moderate-strong staining supports the diagnosis of EFT. In our study, the majority of monophasic synovial sarcomas and precursor B-lymphoblastic lymphomas showed at least moderate nuclear ERG/FLI1 staining. Previous studies reported occasional reactivity of FLI1 monoclonal and polyclonal antibodies with poorly differentiated synovial sarcomas (more relevant to the differential diagnosis of EFTs). In our cohort, only 1 synovial sarcoma was poorly differentiated (which showed focal CD99 staining), whereas all 6 of the remaining 10 monophasic sarcomas evaluated for CD99 staining were strongly positive. Because we did not have additional poorly differentiated synovial sarcomas for evaluation, additional studies will be required to characterize EPR3864 staining in that entity. Similarly, CD99 and FLI1 staining in precursor B-lymphoblastic lymphomas/leukemias is well characterized and represents an important differential diagnostic consideration in EFT evaluation. Differentiating EFTs from these entities, which may show cross-reactivity with all FLI1 antibodies, will likely continue to require a combination of morphology, immunohistochemistry, and molecular studies.

While this study was being conducted, Minner et al60 evaluated EPR3864 staining in 11,483 tumors and 72 normal tissue types and reported strong staining nearly exclusively in prostate carcinoma and vascular tumors; however, they reported no staining in 17 evaluable primitive neuroectodermal tumors. Wang et al61 also recently evaluated EPR3864 staining in 32 EFTs, including 22 with EWSR1:FLI1, 8 with EWSR1:ERG, and 2 with EWSR1-NFATC2. They observed predominantly diffuse moderate to strong staining in 7 of 8 ERG-rearranged cases, but only 3 of 24 non–ERG-rearranged cases showed staining with EPR3864 (all very weak).61 Importantly, Minner et al and Wang et al used substantially different antibody dilutions (1:400 and 1:2,000) compared with our current study, which used ready-to-use, prediluted EPR3864 antibody (1:50-1:100). Our study also used the same pretreatment conditions and automated staining and detection instrumentation as we recently validated in prostate cancer biopsies45 and use clinically at our institution.

Although the availability of molecular techniques has reduced the need for additional immunohistochemistry markers to identify EFTs, EPR3864 shows similar sensitivity to other polyclonal and monoclonal antibodies against FLI1 and has the advantage of being well characterized (in the context of prostate cancer) in its ability to detect ERG, with minimal background staining. Similarly, like other FLI1/ERG antibodies,5,9,56 EPR3864 is a highly sensitive vascular marker,53,60,62 supporting an additional area of diagnostic usefulness (S.A.T., D.R.L., and L.P.K., unpublished observations, 2012).

Additional studies will be needed to directly compare EPR3864 with other FLI1 antibodies, and we are not aware of studies that have investigated whether other currently used antibodies against FLI1 also cross-react with ERG. However, we hypothesize that this is unlikely given the lack of reported usefulness for detection of prostate cancer.

In summary, we demonstrate that EPR3864 is useful for detecting EFTs harboring both EWSR1:FLI1 and EWSR1:ERG gene fusions. With immunohistochemistry, EPR3864 detection of ERG/FLI1 shows high sensitivity for EFTs (>80% with diffuse moderate to strong nuclear staining) and complements CD99 staining. EPR3864 also stains a substantial proportion of Burkitt lymphomas, monophasic synovial sarcomas, and precursor B-lymphoblastic lymphomas/leukemias. In cases in which these entities are included in the differential diagnosis because of morphology, molecular confirmation of EFTs will likely be required. Our results suggest that EPR3864, which has demonstrated usefulness in the diagnosis and molecular subtyping of prostate cancer (which also harbor ETS gene fusions), may also be useful in differentiating EFTs from other SRBCTs.
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