5-3-2022

# ETS-related Gene (ERG) is Differentially Expressed in Dermatofibroma (Fibrous Histiocytoma) as Compared With Dermatofibrosarcoma Protuberans and Hypertrophic Scars: A Pilot Immunohistochemical Study

Meredith Hengy
*Henry Ford Health*, mhengy1@hfhs.org

Jesse Veenstra
*Henry Ford Health*, jveenst1@hfhs.org

Kyle Perry
*Henry Ford Health*, KPERRY4@hfhs.org

David M. Ozog
*Henry Ford Health*, dozog1@hfhs.org

Ben J. Friedman
*Henry Ford Health*, bfriedm1@hfhs.org



## Recommended Citation

Hengy M, Veenstra J, Perry K, Ozog DM, and Friedman BJ. ETS-related Gene (ERG) is Differentially Expressed in Dermatofibroma (Fibrous Histiocytoma) as Compared With Dermatofibrosarcoma Protuberans and Hypertrophic Scars: A Pilot Immunohistochemical Study. Appl Immunohistochem Mol Morphol 2022.

# ETS-related Gene (ERG) is Differentially Expressed in Dermatofibroma (Fibrous Histiocytoma) as Compared With Dermatofibrosarcoma Protuberans and Hypertrophic Scars: A Pilot Immunohistochemical Study

*Meredith Hengy, BASc,* Jesse Veenstra, MD, PhD,† Kyle Perry, MD,‡ David M. Ozog, MD,† and Ben J. Friedman, MD†‡*

**Abstract:** Immunohistochemical staining can be of great utility in differentiating various cutaneous spindle cell neoplasms, particularly when the histomorphologic appearance of the lesions is inconclusive. Nuclear staining for ETS-related gene (ERG), a highly sensitive endothelial cell marker, has seldom been studied in the context of cutaneous spindle cell neoplasms. Little is known about its specificity for vascular differentiation. In this pilot study, immunohistochemical analysis for ERG was performed on 15 dermatofibromas (DF), 10 keloids, and 9 dermatofibrosarcoma protuberans (DFSP) tumors. Consistent nuclear expression of ERG was found in DF [100% (15/15) of the lesions demonstrated > 50% labeling of tumor cells with moderate to strong intensity]. However, ERG expression was largely absent in DFSP [89% (8/9) of the lesions demonstrating <50% labeling staining, generally of mild intensity] and hypertrophic scars-keloids [80% (8/10) without expression]. On the basis of the results of this pilot study, immunohistochemical staining for ERG may prove useful in helping to differentiate DF from DFSP and hypertrophic scars in the context of partial biopsy sampling. If replicated in a larger number of samples, this finding could mitigate the use of costly sequencing panels and potentially avoid unnecessary reexcisions in certain contexts.

**Key Words:** ETS-family transcription factor, ERG, immunohistochemistry, dermatofibroma, fibrous histiocytoma

(*Appl Immunohistochem Mol Morphol* 2022;00:000–000)

Dermal-based spindled cell neoplasms comprise a heterogeneous group of tumors arising from divergent cell lineages. These are characterized by the presence of elongated cells in various configurations on light microscopy.[1] Similar to their soft tissue counterparts, these neoplasms may demonstrate either benign, intermediate-grade, or malignant phenotypes.[2] Dermatofibroma (DF), also known as fibrous histiocytoma, is the most commonly encountered benign cutaneous mesenchymal tumor. Malignant spindled cell sarcomas in the skin are much more infrequent (< 1% of malignant tumors in the skin), with the most common being dermatofibrosarcoma protuberans (DFSP), pleomorphic dermal sarcoma, and leiomyosarcoma.[1] A pattern-based diagnostic approach is often taken when differentiating these neoplasms, which includes consideration of tumor location, architectural features such as size, depth, stroma, cellular configuration, and cytomorphology.[1,3] These parameters alone are usually sufficient for the distinction between various entities, though immunohistochemical staining is not infrequently required for additional diagnostic support.[4]

ERG is the nuclear protein product of the ETS-related gene (ERG), which serves as a transcriptional regulator and affects angiogenesis and endothelial cell migration.[5,6] ERG as an immunohistochemical stain has several uses in clinical practice, most notably serving as a highly sensitive endothelial cell marker.[7] It also exhibits positive staining in several chondrogenic tumors, prostate

**TABLE 1.** Patient Demographics and Lesion Locations

| Tissue Type | Mean Age (± SD) | Sex | Location Frequency (%) |
|---|---|---|---|
| Dermatofibroma (n = 15) | 45 (± 15.2) | M: 3<br>F: 12 | Thigh (40%)<br>Lower leg (13%)<br>Forearm (20%)<br>Hip (7%)<br>Cheek (7%)<br>Shoulder/back (13%) |
| Keloid (n = 10) | 32 (± 17.9) | M: 3<br>F: 7 | Helix (40%)<br>Earlobe (50%)<br>Jaw (10%) |
| Dermatofibrosarcoma protuberans (n = 9) | 45 (± 12.6) | M: 4<br>F: 5 | Shoulder/back (56%)<br>Scalp (11%)<br>Thigh/buttock (22%)<br>Abdominal wall (11%) |

F indicates female; M, male.

Received for publication December 22, 2021; accepted March 22, 2022.
From the *Wayne St. University School of Medicine; Departments of †Dermatology; and ‡Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, MI.
The authors declare no conflict of interest.
Reprints: Ben J. Friedman, MD, 3031 West Grand Blvd., Suite 800, Detroit, MI 48202 (e-mail: bfriedm1@hfhs.org).

adenocarcinomas, and other tumors with ERG gene rearrangements (eg, ERG-rearranged Ewing sarcoma).[8–12] Currently, the use of ERG in dermatopathology has primarily been limited to supporting vascular differentiation. However, strong and diffuse nuclear expression of ERG has recently been reported in the setting of EWSR1-SMAD3 rearranged fibroblastic tumor (ESFT), a newly described superficial-acral spindle cell neoplasm.[13,14] Similarly, diffuse

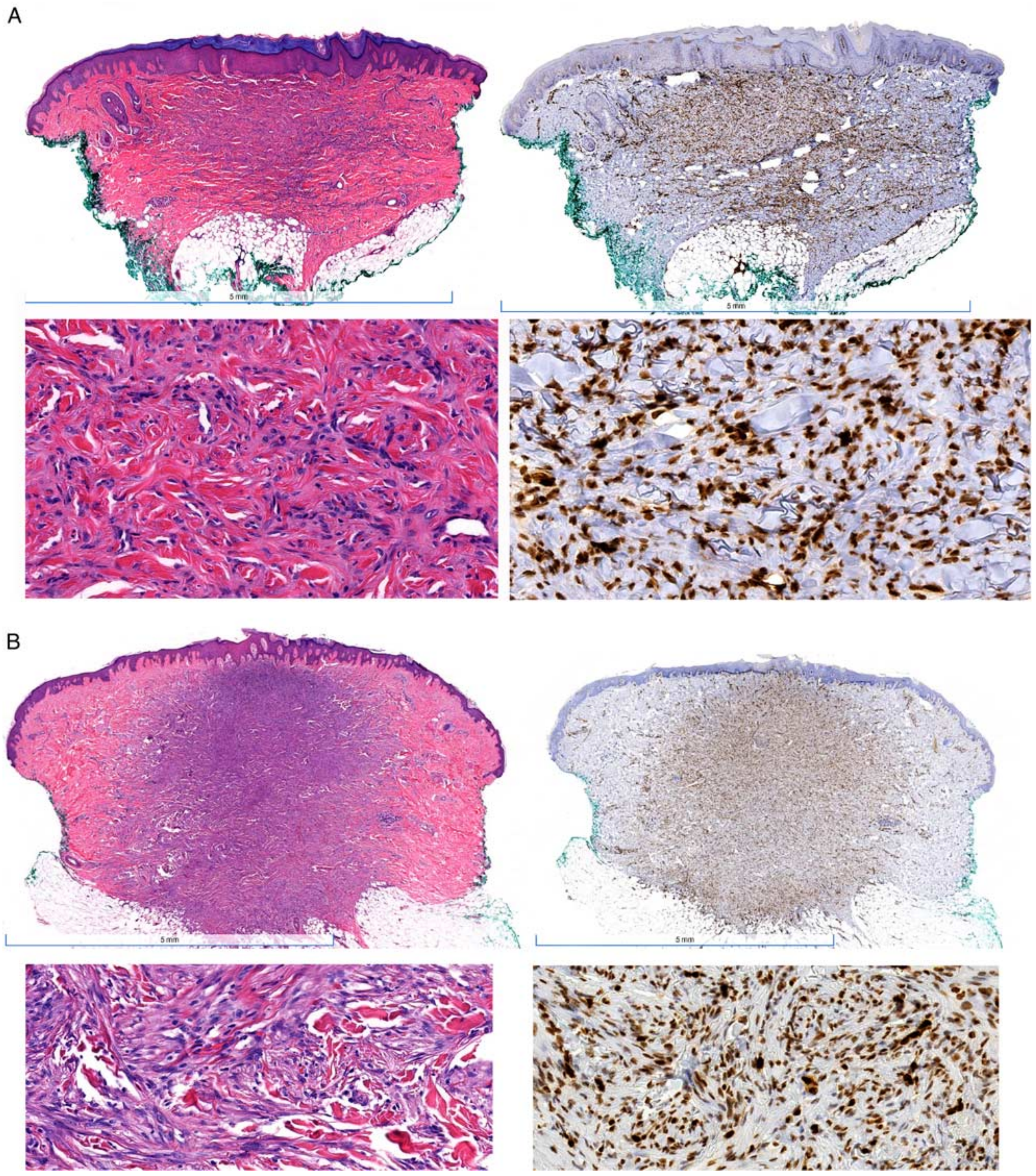


**FIGURE 1.** ERG staining of dermatofibroma. A, Conventional-type dermatofibroma. ERG immunohistochemistry: > 50% staining (S3) is demonstrated with strong intensity (I3). B, Cellular-type dermatofibroma. ERG immunohistochemistry: > 50% staining (S3) is demonstrated with strong intensity (I3). Left: hematoxylin and eosin (×40 and ×200 original magnification). Right: immunohistochemical staining for ERG (×40 and ×200 original magnification).

staining for ERG has been reported in a few case studies of pseudomyogenic hemangioendothelioma and epithelioid sarcoma.[15–17] With these few exceptions, data regarding its overall specificity for vascular differentiation in the setting of commonly encountered cutaneous spindle cell neoplasms is lacking.

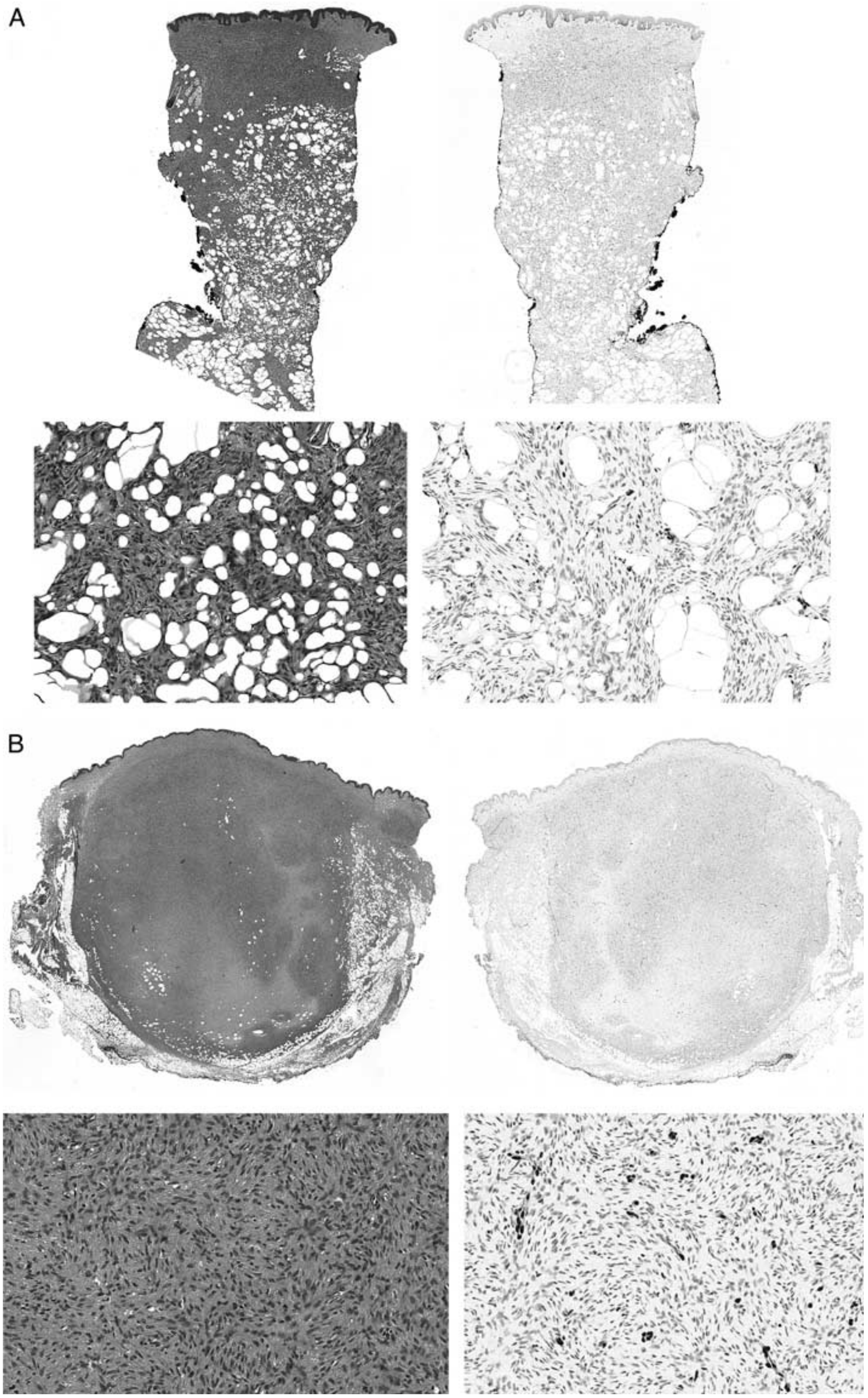


**FIGURE 2.** ERG staining of dermatofibrosarcoma protuberans. A and B, Two representative dermatofibrosarcoma protuberans biopsies. For both cases, ERG is positive in <10% of cells (S1) with low intensity (I1). Left: hematoxylin and eosin (×25 and ×100 original magnification). Right: immunohistochemical staining for ERG (×25 and ×100 original magnification).

Our group recently reported a case of cellular DF arising on an acral surface that demonstrated strong nuclear expression of ERG, but ancillary testing failed to detect an EWSR1-SMAD3 fusion.[18] This result further questions the specificity of ERG for vascular tumors and provides the basis for the current study. In this pilot study, the expression pattern of ERG was explored in a larger sample of conventional and cellular forms of cutaneous DFs to see if our prior finding was reproducible. In addition, similiar numbers of hypertrophic scars-keloids and DFSPs were stained as control comparators.

## MATERIALS AND METHODS

After institutional review board approval (#15028), immunohistochemical analysis for ERG (EP111, prediluted, Dako) was performed on 15, sequentially encountered cases of DF (both conventional and cellular types) from routine

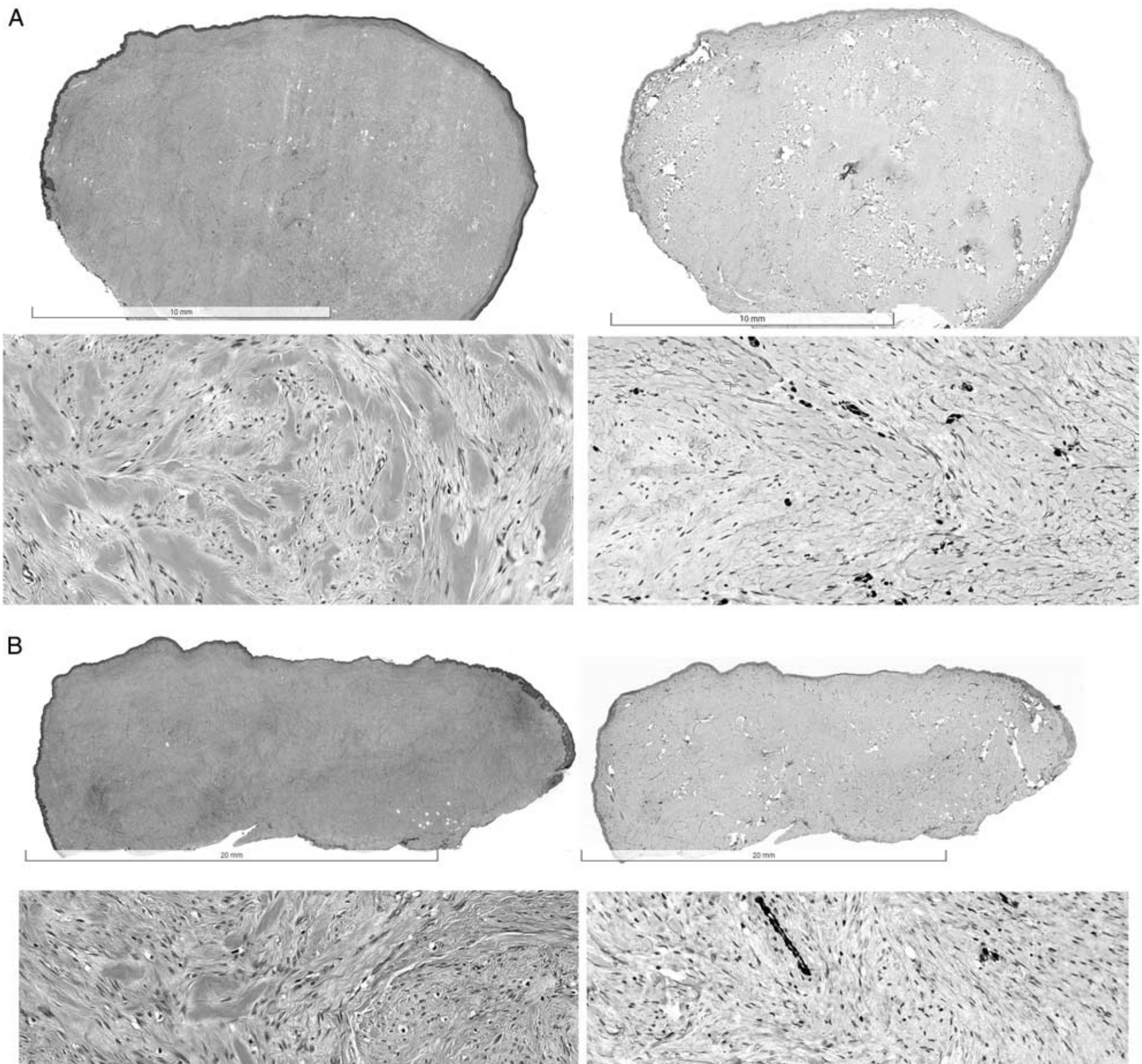


**FIGURE 3.** ERG staining of hypertrophic-keloid scars. A and B, Two representative keloid biopsies. No appreciable ERG expression. Left: hematoxylin and eosin (×40 and ×200 original magnification). Right: immunohistochemical staining for ERG (×40 and ×200 original magnification).

 

clinical practice. Only cases in which the bulk of the tumor was captured in the biopsy or excision specimens were assessed. Ten keloid scars and 9 DFSPs were also stained. Slides were prepared on a PT Link and Autostainer Link 48 (Dako). The primary antibody was visualized using peroxidase as a detection system (Dako). ERG protein showed nuclear localization. Immunoreactivity was scored as percentage positivity (S0: no staining, S1: <10% staining, S2: 10% to 50% staining, S3: > 50% staining) and intensity (I0: none, I1: mild, I2: moderate, I3: strong).[19] The nuclear staining intensity of normal endothelial cells was used as a positive control, as has been previously described.[20] Descriptive statistical analyses were performed using Microsoft Excel software.

## RESULTS

Immunohistochemical analysis for ERG was performed on 15 DFs, 10 keloids, and 9 DFSPs. Patient age, sex, and tumor location for all 3 neoplasm-types were consistent with characteristic findings for these lesions (Table 1). Biopsies of all 3 entities revealed classic histomorphologic features on hematoxylin and eosin staining (Figs. 1–3). Conventional DFs demonstrated plate-like epidermal acanthosis overlying a heavily collagenized dermis containing interstitial stellate-appearing spindled cells with peripheral collagen trapping. Cellular DFs contained similar epidermal changes and peripheral collagen trapping but with a more tightly packed and often fascicular arrangement of plumper spindled cells. DFSPs were characterized by a storiform arrangement of tightly packed monomorphous-spindled cells with extension into the fat lobules. Hypertrophic scars-keloids demonstrated a haphazard arrangement of heavily collagenized and edematous fascicles with few interweaving fibroblasts and myofibroblasts.

Consistent nuclear expression of ERG was found in DFs, with all 15 specimens demonstrating > 50% of staining (S3). There was variability in the intensity of the staining with over half the DF specimens displaying a strong pattern (I3) (8/15, 53%), 33% demonstrating a moderate pattern (I2) (5/15), and 13% demonstrating a weak pattern (I1) (2/15) (Figs. 1, 4). DFSPs demonstrated no staining (S0) in a third of the specimens (3/9, 33%), <10% staining in 22% of the specimens (2/9), 10% to 50% staining in 33% of specimens (3/10), and > 50% staining in 11% of specimens (1/9). For DFSPs with positive staining, the intensity was mild (I1) for all lesions (Figs. 2, 4). In keloids, no staining (S0) was found in 8/10 (80%) of the tissue specimens, with the remaining 2/10 displaying <10% staining (S1) of mild intensity (I1) (Figs. 3, 4).

## DISCUSSION

DF, the most commonly encountered cutaneous mesenchymal spindle cell neoplasm, is most often diagnosed based on histomorphologic criteria alone. Numerous subtypes have been recognized, including conventional, cellular, hemosiderotic, aneurysmal, heavily lipidized, deep variant, and atypical (with monster cells).[21–26] The histologic differential diagnosis most commonly includes DFSP, dermatomyofibroma, hypomelanotic blue nevus, and scar.

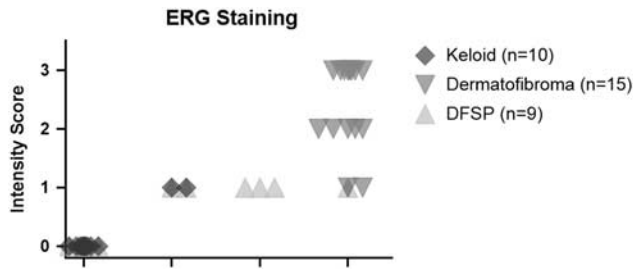


**FIGURE 4.** ERG immunoreactivity as demonstrated by intensity and percent positivity. Dermatofibromas consistently demonstrated high ERG positivity of > 50% staining regardless of intensity score, with all lesions having an intensity score of 1 or greater, compared with keloids and dermatofibrosarcoma protuberans. DFSP indicates dermatofibrosarcoma protuberans.

Immunohistochemistry is seldom necessary but can be useful in superficially sampled specimens precluding complete architectural evaluation. Panels with some combination of: myogenic markers (smooth muscle actin, desmin), endothelial markers (CD31), melanocytic markers (HMB-45, Melan-A), and other markers: (Factor 13a, CD34, Stromelysin 3, D2-40) have historically been used to help distinguish between DF and other potential mimickers.[4,27]

In particular, differentiating DF from DFSP can occasionally be problematic despite the utility of the above markers. There is a tendency for DF to express CD34 at its periphery and lose expression of Factor 13a in its cellular forms, making a distinction from DFSP challenging.[28] Moreover, rare cases of DFSP may lose CD34 expression, most commonly in the context of fibrosarcomatous transformation.[29] In recent years, there has been increased utilization of next-generation sequencing panels to confirm the presence of relevant fusions in this context (such as *COL1A1-PDGFB*) to increase diagnostic accuracy. However, these assays remain costly and are not readily available in many small community-based practices.

In this small pilot study, we found that DFs demonstrate consistent immunohistochemical expression of ERG. This was in contrast to DFSP and hypertrophic-keloidal scars, which demonstrated negligible expression based on both percent positivity and staining intensity. This finding is significant for several reasons: first, the skin-derived cell of origin in DF and DFSP remains largely unknown. The presence of strong ERG expression in DF might imply that this tumor is derived from a pluripotent stem cell with the potential to proceed down an endothelial or fibrohistiocytic pathway (with trauma perhaps activating the latter). On the other hand, DFSP is thought to originate from an undifferentiated mesenchymal stem cell with neurologic, muscular, and fibroblastic components or from a dermal stem cell.[30] The negligible expression of ERG in DFSP evident in this study lends further support to the hypothesis that these 2 tumors are more distinct than they are similar in regards to their biological derivation.

ERG may prove to be a useful stain in the clinical setting of a partial biopsy specimen when DF and DFSP are both considerations based on histomorphology. In addition, the newly described acral-spindled cell ESFT may not be unique in its expression of ERG and could theoretically exist on the spectrum of fibrous histiocytoma, albeit with an additional characteristic genetic event more likely to occur on an acral site. Finally, the lack of unique ERG expression in ESFT demonstrates that ERG staining may not be a helpful adjunct in differentiating this entity from other cutaneous spindle cell neoplasms. Limitations of this study are its small sample size, particularly the fewer cases of DFSP examined. In addition, only 2 variants of DF were analyzed. Further studies with larger cohorts and assessment of additional DF variants will be required to validate these findings.

## REFERENCES


1. Choi JH, Ro JY. Cutaneous spindle cell neoplasms: pattern-based diagnostic approach. *Arch Pathol Lab Med*. 2018;142:958–972.
2. Magro G. Differential diagnosis of benign spindle cell lesions. *Surg Pathol Clin*. 2018;11:91–121.
3. Hollmig ST, Sachdev R, Cockerell CJ, et al. Spindle cell neoplasms encountered in dermatologic surgery: a review. *Dermatol Surg*. 2012;38: 825–850.
4. Metgud R, Naik S, Patel S. Spindle cell lesions: a review on immunohistochemical markers. *J Cancer Res Ther*. 2017;13:412–418.
5. Haber MA, Iranmahboob A, Thomas C, et al. ERG is a novel and reliable marker for endothelial cells in central nervous system tumors. *Clin Neuropathol*. 2015;34:117–127.
6. Birdsey GM, Dryden NH, Shah AV, et al. The transcription factor Erg regulates expression of histone deacetylase 6 and multiple pathways involved in endothelial cell migration and angiogenesis. *Blood*. 2012;119:894–903.
7. Nikolova-Krstevski V, Yuan L, Le Bras A, et al. ERG is required for the differentiation of embryonic stem cells along the endothelial lineage. *BMC Dev Biol*. 2009;9:72.
8. Shon W, Folpe AL, Fritchie KJ. ERG expression in chondrogenic bone and soft tissue tumours. *J Clin Pathol*. 2015;68:125–129.
9. Zhou E, Zhang B, Zhu K, et al. A TMPRSS2-ERG gene signature predicts prognosis of patients with prostate adenocarcinoma. *Clin Transl Med*. 2020;10:e216.
10. Pflueger D, Rickman DS, Sboner A, et al. N-myc downstream regulated gene 1 (NDRG1) is fused to ERG in prostate cancer. *Neoplasia*. 2009;11:804–811.
11. Shing DC, McMullan DJ, Roberts P, et al. FUS/ERG gene fusions in Ewing's tumors. *Cancer Res*. 2003;63:4568–4576.
12. Moore SD, Offor O, Ferry JA, et al. ELF4 is fused to ERG in a case of acute myeloid leukemia with a t(X;21)(q25-26;q22). *Leuk Res*. 2006;30:1037–1042.
13. Habeeb O, Korty KE, Azzato EM, et al. EWSR1-SMAD3 rearranged fibroblastic tumor: case series and review. *J Cutan Pathol*. 2021;48:255–262.
14. Kao YC, Flucke U, Eijkelenboom A, et al. Novel EWSR1-SMAD3 gene fusions in a group of acral fibroblastic spindle cell neoplasms. *Am J Surg Pathol*. 2018;42:522–528.
15. Ansai SI, Morimoto M, Akaishi S. Pseudomyogenic hemangioendothelioma. *J Nippon Med Sch*. 2019;86:126–130.
16. Stuart LN, Gardner JM, Lauer SR, et al. Epithelioid sarcoma-like (pseudomyogenic) hemangioendothelioma, clinically mimicking dermatofibroma, diagnosed by skin biopsy in a 30-year-old man. *J Cutan Pathol*. 2013;40:909–913.
17. Miettinen M, Wang Z, Sarlomo-Rikala M, et al. ERG expression in epithelioid sarcoma: a diagnostic pitfall. *Am J Surg Pathol*. 2013;37: 1580–1585.
18. Friedman BJ. Pitfall regarding expression of ETS-related gene (ERG) in fibrohistiocytic neoplasms. *J Cutan Pathol*. 2021;48: 1003–1004.
19. Ayala G, Frolov A, Chatterjee D, et al. Expression of ERG protein in prostate cancer: variability and biological correlates. *Endocr Relat Cancer*. 2015;22:277–287.
20. Park K, Tomlins SA, Mudaliar KM, et al. Antibody-based detection of ERG rearrangement-positive prostate cancer. *Neoplasia*. 2010;12: 590–598.
21. Santa Cruz DJ, Kyriakos M. Aneurysmal ("angiomatoid") fibrous histiocytoma of the skin. *Cancer*. 1981;47:2053–2061.
22. Calonje E, Mentzel T, Fletcher CD. Cellular benign fibrous histiocytoma. Clinicopathologic analysis of 74 cases of a distinctive variant of cutaneous fibrous histiocytoma with frequent recurrence. *Am J Surg Pathol*. 1994;18:668–676.
23. Singh Gomez C, Calonje E, Fletcher CD. Epithelioid benign fibrous histiocytoma of skin: clinico-pathological analysis of 20 cases of a poorly known variant. *Histopathology*. 1994;24:123–129.
24. Kaddu S, McMenamin ME, Fletcher CD. Atypical fibrous histiocytoma of the skin: clinicopathologic analysis of 59 cases with evidence of infrequent metastasis. *Am J Surg Pathol*. 2002;26:35–46.
25. Cohen PR, Erickson CP, Calame A. Atrophic dermatofibroma: a comprehensive literature review. *Dermatol Ther (Heidelb)*. 2019;9: 449–468.
26. Iwata J, Fletcher CD. Lipidized fibrous histiocytoma: clinicopathologic analysis of 22 cases. *Am J Dermatopathol*. 2000;22:126–134.
27. Cribier B, Noacco G, Peltre B, et al. Stromelysin 3 expression: a useful marker for the differential diagnosis dermatofibroma versus dermatofibrosarcoma protuberans. *J Am Acad Dermatol*. 2002;46: 408–413.
28. Bandarchi B, Ma L, Marginean C, et al. D2-40, a novel immunohistochemical marker in differentiating dermatofibroma from dermatofibrosarcoma protuberans. *Mod Pathol*. 2010;23: 434–438.
29. Sato N, Kimura K, Tomita Y. Recurrent dermatofibrosarcoma protuberans with myxoid and fibrosarcomatous changes paralleled by loss of CD34 expression. *J Dermatol*. 1995;22:665–672.
30. Song JS, Kim EJ, Park CS, et al. Dermatofibrosarcoma protuberans: an immunomarker study of 57 cases that included putative mesenchymal stem cell markers. *Appl Immunohistochem Mol Morphol*. 2017;25:586–591.