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Gains of *COL1A1-PDGFB* genomic copies occur in fibrosarcomatous transformation of dermatofibrosarcoma protuberans

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Dermatofibrosarcoma protuberans is a superficial low-grade sarcoma that rarely evolves into a high-grade fibrosarcoma. Dermatofibrosarcoma protuberans is genetically characterized by the unbalanced chromosomal t(17;22)(q21;q13), usually in the form of a supernumerary ring chromosome. The product of this chromosomal translocation is the chimeric gene *COL1A1-PDGFB* (collagen type I alpha I-platelet-derived growth factor beta), which is amplified at low levels in the ring chromosome. The aims of this study were to evaluate (1) whether genomic gains of this fusion gene occur during the clonal evolution of dermatofibrosarcoma protuberans into fibrosarcomatous dermatofibrosarcoma protuberans and (2) whether there is a difference between the number of genomic copies of *COL1A1-PDGFB* between classic dermatofibrosarcoma protuberans and dermatofibrosarcoma protuberans areas associated with fibrosarcomatous dermatofibrosarcoma protuberans. Eleven cases of fibrosarcomatous dermatofibrosarcoma protuberans with both dermatofibrosarcoma protuberans and fibrosarcomatous areas and 10 cases of classic dermatofibrosarcoma protuberans were studied. Genomic copies of *COL1A1-PDGFB* were evaluated by fluorescence *in situ* hybridization using a custom designed probe for the *PDGFB* locus on 4 μm thick paraffin-embedded tissue sections. Genomic gains of the *COL1A1-PDGFB* gene were observed in six (of 10) fibrosarcomatous dermatofibrosarcoma protuberans in the fibrosarcomatous areas when compared to the dermatofibrosarcoma protuberans areas of the same tumor (2–7 gene copies (median *PDGFB* copy gain, 2.8) versus 1–3 gene copies (median *PDGFB* copy gain, 1.7), respectively, $P = 0.004$). Four fibrosarcomatous dermatofibrosarcoma protuberans did not show genomic gains of *COL1A1-PDGFB* fusion gene between the two areas. Essentially no difference in the copy number of *COL1A1-PDGFB* fusion gene was observed between dermatofibrosarcoma protuberans areas of classic dermatofibrosarcoma protuberans and dermatofibrosarcoma protuberans areas of fibrosarcomatous dermatofibrosarcoma protuberans (median *PDGFB* copy gain of 1.8 versus 1.7, respectively, $P = 0.36$). Genomic gains of *COL1A1-PDGFB* fusion gene is possibly an oncogenic mechanism that is identified in the clonal evolution of a subset of dermatofibrosarcoma protuberans that evolves into fibrosarcomatous dermatofibrosarcoma protuberans. Since this finding was not observed in all cases of fibrosarcomatous dermatofibrosarcoma protuberans, other oncogenic mechanisms may be operating in this form of tumor progression. Copy number of *COL1A1-PDGFB* fusion gene in the classic dermatofibrosarcoma protuberans areas does not seem to be a major predisposing mechanism for fibrosarcomatous transformation.
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Dermatofibrosarcoma protuberans is a locally aggressive dermal and subcutaneous tumor, which has very small risk of metastases.[1] Fibrosarcomatous transformation rarely occurs in dermatofibrosarcoma protuberans and is associated with an increased risk for metastases.[2,3] Current treatment for dermatofibrosarcoma protuberans or fibrosarcomatous dermatofibrosarcoma protuberans consists of wide local excision with negative margins and possible adjuvant radiotherapy in selected cases.[4,5]

Dermatofibrosarcoma protuberans is cytogenetically characterized by an unbalanced chromosomal translocation t(17;22)(q22;q13), usually presenting as a supernumerary ring chromosome containing genomic sequences of both chromosome 17 and 22.[6–8] The result of this chromosomal translocation is the creation of a fusion gene with sequences from

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collagen type I alpha I (*COL1A1*) on chromosome 17q22 fused to the platelet-derived growth factor beta (*PDGFB*) on chromosome 22q13. The fusion product *COL1A1-PDGFB* is amplified at low levels on the ring chromosome (1–3 copies) and its protein product creates an autocrine loop with increased PDGFRB activity.[9–11]

Early case reports examining the cytogenetic alterations within fibrosarcomatous dermatofibrosarcoma protuberans indicate that the *COL1A1-PDGFB* fusion product is present in both fibrosarcomatous and dermatofibrosarcoma protuberans areas, indicating a common genetic origin for the two tumor components.[12] However, a single previous study was not able to find a difference in copy numbers between fibrosarcomatous and dermatofibrosarcoma protuberans areas using comparative genomic hybridization.[13] The objective of our study was to evaluate whether genomic gains of the *COL1A1-PDGFB* fusion gene occur during the clonal evolution of dermatofibrosarcoma protuberans into fibrosarcomatous dermatofibrosarcoma protuberans using fluorescence *in situ* hybridization. In addition, we aimed to determine if there was a difference between the number of *COL1A1-PDGFB* gene fusion copies between cases of classic dermatofibrosarcoma protuberans and dermatofibrosarcoma protuberans areas associated with fibrosarcomatous transformation.

Materials and methods

Patient Data

Eleven cases of fibrosarcomatous transformation of dermatofibrosarcoma protuberans, 10 of which with distinctly identifiable dermatofibrosarcoma protuberans and fibrosarcomatous areas, were examined from the extramural consultation files of the Department of Laboratory Medicine and Pathology at Mayo Clinic in Rochester, Minnesota, after Mayo Foundation Institutional Review Board approval. Ten cases of classic dermatofibrosarcoma protuberans were also examined from both intramural and extramural sources. In each case, 4 μm-thick sections of formalin-fixed, paraffin-embedded material were stained with hematoxylin and eosin and reviewed to confirm the diagnosis and correlate with fluorescence *in situ* hybridization results (see below).

Fluorescence *In Situ* Hybridization

BAC clones flanking the *PDGFB* locus on chromosome 22q13 were obtained from Children's Hospital Oakland Research Institute (Oakland, CA, USA). DNA isolation was performed according to Qiagen plasmid Maxi Kit specifications. DNA was directly labeled using nick translation kit from Abbot Laboratory using the Spectrum Orange and Spectrum Green fluorochromoes (Vysis Inc., Downers Grove, IL, USA).

Interphase molecular cytogenetic studies were performed on 4 μm paraffin-embedded thin tissue sections that were deparaffinized in xylene (2 $\times$ 15 min), dehydrated twice in 100% in ethylic alcohol for 5 min, and treated with 10 mmol/l citric acid for 10 min in a humid microwave. Tissue sections were then transferred to 37°C 2 $\times$ SSC for 5 min and protein digested with Digest All-3 (Zymed, San Francisco, CA, USA). After brief washing in 1 $\times$ PBS, the slides were sequentially dehydrated in alcohol (70, 85 and 100%) and air-dried at room temperature. Tissue sections were denatured at 80°C for 5 min and BAC probe hybridization was carried out overnight in a humidified chamber at 37°C. Tissue sections were then washed in 0.1% NP40/2 $\times$ SSC at 76°C for 4 min, then washed in 0.1% NP40/2 $\times$ SSC at room temperature for 1 min. Slides were then mounted in VACTASHIELD mounting medium with 1.5 μg/ml of 4′,6-diamidino-2-phenylindole. Tumor samples were scored by three investigators in approximately 300–1000 cells within both the dermatofibrosarcoma protuberans and fibrosarcomatous areas. Two different counting techniques were used: (1) green and orange signals were tallied in individual cells; and (2) signals were counted individually in a high power fields ($\times$1000) and ratios of green to red signals were tallied. The *COL1A1-PDGFB* copy gain represents the average copy gain of the fusion gene per cell and was calculated by subtracting green signals from red signals and dividing by total number of cells counted.

Statistical Analysis

All group comparisons were performed using the Wilcoxon test. Paired analysis between dermatofibrosarcoma protuberans and fibrosarcomatous areas was performed with the Wilcoxon paired signed rank test. Level of significance was set at $P \leq 0.05$ (two tailed).

Results

Clinicopathologic Features

Clinical characteristics of the study group are listed in Table 1. On histologic examination (Figure 1), all tumors had a dermatofibrosarcoma protuberans component characterized by a uniform, low-grade spindle cell proliferation growing in a storiform pattern and in an infiltrative manner (Figure 1a). Mitotic counts in this area ranged from 0 to 2 mitoses/10 high-power fields. Case 9 also had a confirmed dermatofibrosarcoma protuberans component but the block was not available for further study. High-grade fibrosarcomatous areas were present in all 11 cases and consisted of markedly

Table 1 Clinical features and fluorescence *in situ* hybridization results of the dermatofibrosarcoma protuberans and fibrosarcomatous area of fibrosarcomatous dermatofibrosarcoma protuberans cases and of classic dermatofibrosarcoma protuberans controls

Case	*Age*	*Gender*	*Location*	*Dermatofibrosarcoma protuberans area COL1A1-PDGFB copy gain*	*Fibrosarcomatous area COL1A1-PDGFB copy gain*
Fibrosarcomatous dermatofibrosarcoma protuberans					
1	22	F	Scalp	1.2	2.8
2	100	F	Back	2.1	3.4
3	50	F	Chest	0.5	0.8
4	50	M	Chest	2.3	4.0
5	35	M	Chest	1.3	3.1
6	22	F	Chest	1.6	2.1
7	85	M	Back	2.7	5.9
8	73	F	Arm	0.2	0.1
9	66	M	Back	N/A	2.8
10	51	M	Neck	2.8	4.7
11	54	F	Face	1.8	2.0
Classic dermatofibrosarcoma protuberans (controls)					
A	32	F	Shoulder	1.5	
B	45	M	Face	2.3	
C	43	F	Chest	1.8	
D	44	F	Back	1.7	
E	40	F	Shoulder	2.4	
F	60	M	Face	1.8	
G	43	F	Shoulder	1.6	
H	34	M	Thigh	1.7	
I	42	F	Thigh	2.4	
J	56	F	Shoulder	2.3	

COL1A1-PDGFB copy gain, represents an average copy gain of the fusion gene per cell counted. N/A, not applicable.

cellular areas with a herringbone pattern of growth and an increased mitotic rate (Figure 1b).

Fluorescence *In Situ* Hybridization

Genomic gains of the *COL1A1-PDGFB* gene were observed in six (of 10) cases of fibrosarcomatous dermatofibrosarcoma protuberans in the fibrosarcomatous areas when compared to the classic dermatofibrosarcoma protuberans areas paired for individual cases ($P = 0.004$) (Table 1 and Figure 2). The median *COL1A1-PDGFB* copy gain in dermatofibrosarcoma protuberans areas of fibrosarcomatous dermatofibrosarcoma protuberans was 1.7 (range 0.2–2.8) (Figure 1d) while the median *COL1A1-PDGFB* copy gain in fibrosarcomatous areas of fibrosarcomatous dermatofibrosarcoma protuberans was 2.8 (range 0–5.9) (Figure 1c). Four (of 10) cases of fibrosarcomatous dermatofibrosarcoma protuberans showed no difference in *COL1A1-PDGFB* copy gains between the fibrosarcomatous areas and dermatofibrosarcoma protuberans areas.

A very small difference in *COL1A1-PDGFB* copy number gains was observed in cases of classic dermatofibrosarcoma protuberans and the dermatofibrosarcoma protuberans areas of fibrosarcomatous dermatofibrosarcoma protuberans but the changes were not statistically significant ($P = 0.36$) (Table 1 and Figure 2). The median *COL1A1-PDGFB* copy gain in classic dermatofibrosarcoma protuberans was 1.8 (range 0–2.4) while the median *COL1A1-PDGFB* copy gain in dermatofibrosarcoma protuberans areas of fibrosarcomatous dermatofibrosarcoma protuberans was 1.7 (range 0.2–2.8).

Metastatic Fibrosarcomatous Dermatofibrosarcoma Protuberans

A single case (case 11) of fibrosarcomatous dermatofibrosarcoma protuberans metastasized to distant bone and morphologically showed 100% fibrosarcomatous differentiation. The metastatic lesion possessed an average *COL1A1-PDGFB* copy number gain of 2.1, but this number was essentially the same as the 2.0 average copy number gain in the fibrosarcomatous area of the primary lesion (Table 1).

Discussion

Fibrosarcomatous change in dermatofibrosarcoma protuberans has been increasingly recognized as a form of tumor progression that carries an increased risk of metastasis over classic dermatofibrosarcoma protuberans, but[2,3,14] the biologic mechanisms underlying this transformation are poorly understood. Prior studies have highlighted the role of increased proliferation rates and *TP53* mutations in the pathogenesis of fibrosarcomatous change in

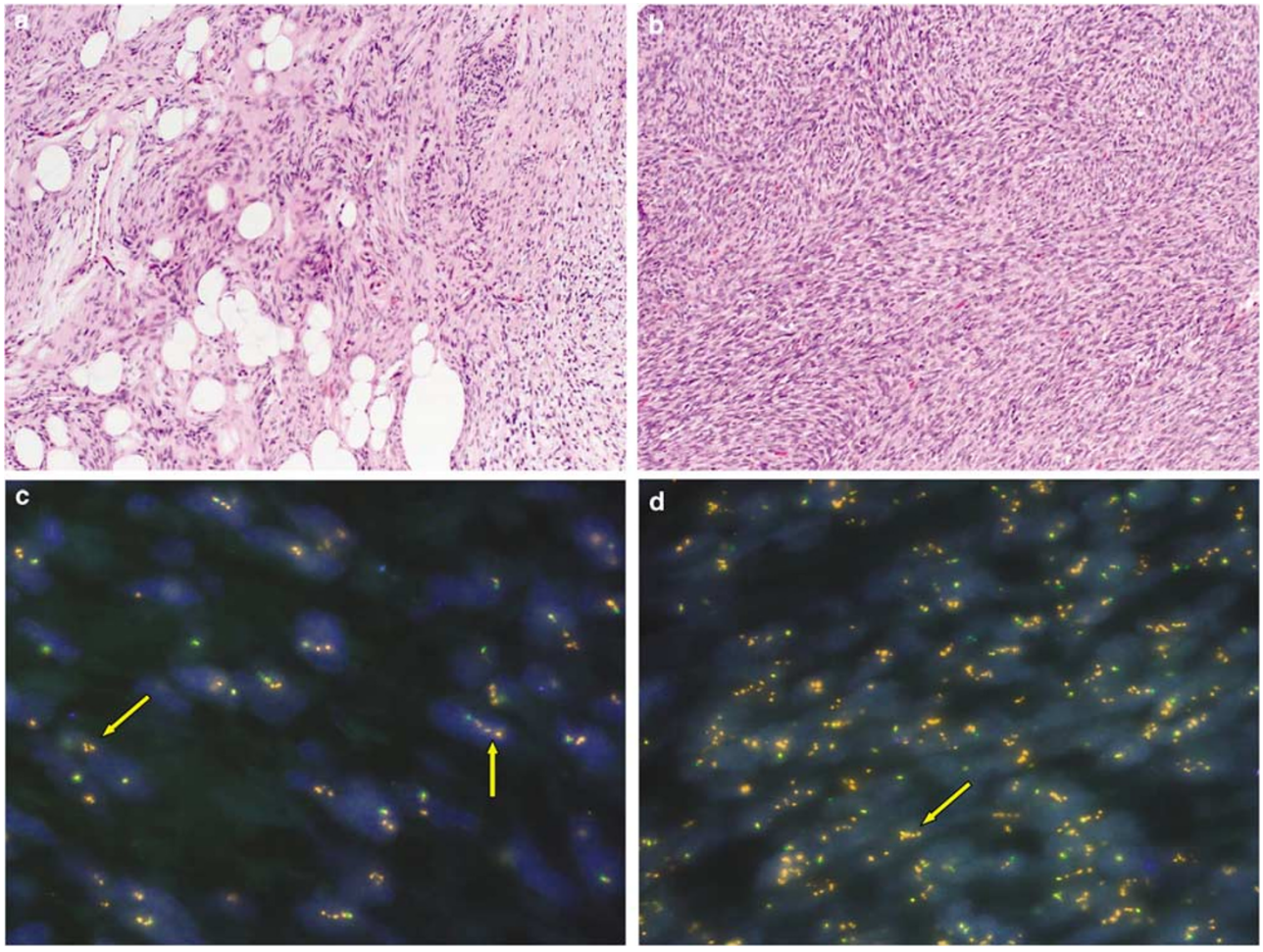

Figure 1 Case 7. (**a**) Excision of a superficial tumor from the back of an 85-year-old male shows a classic dermatofibrosarcoma protuberans; a cellular spindle cell tumor diffusely infiltrating the deep dermis and subcutaneous fat with formation of a storiform architectural pattern (H&E; original magnification ×100). (**b**) The fibrosarcomatous region from the same tumor shows a 'herringbone' fascicular architecture, increased cellularity, and increased mitotic activity (H&E; original magnification ×100). (**c**) Fluorescence *in situ* hybridization of the dermatofibrosarcoma protuberans component of the tumor using a custom designed breakapart probe to the *PDGFB* locus on chromosome 22q13 shows several tumor cells with 1 red–green signal indicating a normal chromosome 22 and 1–3 extra copies of red signal representing *COL1A1-PDGFB* fusion gene (arrows) (original magnification, ×1000). (**d**) Fluorescence *in situ* hybridization of the fibrosarcomatous component of the tumor using a custom designed breakapart probe to the *PDGFB* locus on chromosome 22q13 shows several tumor cells with 1 red–green signal indicating a normal chromosome 22 and 3–7 extra copies of red signal representing *COL1A1-PDGFB* fusion gene (arrow) (original magnification, ×1000).

dermatofibrosarcoma protuberans.[2,15–17] In addition, other studies on fibrosarcomatous dermatofibrosarcoma protuberans have shown that the *COL1A1-PDGFB* fusion gene is present in both dermatofibrosarcoma protuberans and fibrosarcomatous areas.[6,18] Wang *et al*[12] detected the presence of the *COL1A1-PDGFB* fusion gene in five of six cases studied by laser microdissection and reverse transcriptase PCR. Kiuru-Kuhlefelt *et al*[13] used comparative genomic hybridization to analyze DNA copy number changes in the 17q and 22q regions and found an increase in copy number changes between dermatofibrosarcoma protuberans and fibrosarcomatous dermatofibrosarcoma protuberans, although the change was not statistically significant.

The results of our study support the hypothesis that gains in copy number of the *COL1A1-PDGFB* fusion gene may contribute to the fibrosarcomatous change in dermatofibrosarcoma protuberans in a subset of tumors since we identified six of 10 patients (60%) with fibrosarcomatous dermatofibrosarcoma protuberans that had statistically significant genomic gains of the *COL1A1-PDGFB* fusion gene in the fibrosarcomatous area over the dermatofibrosarcoma protuberans area. Our data also confirm the trend noted by Kiuru-Kuhlefelt, who used CGH to find a small increase in copy number changes of chromosome 17 and 22 material in a study set of similar size to our present study.[13] Their data did not reach statistical significance and this finding not only reflects the difficulty CGH would have in detecting subtle changes of copy number but also that combining together cases that operate with and without gains of *COL1A1-PDGFB* in a nonpaired

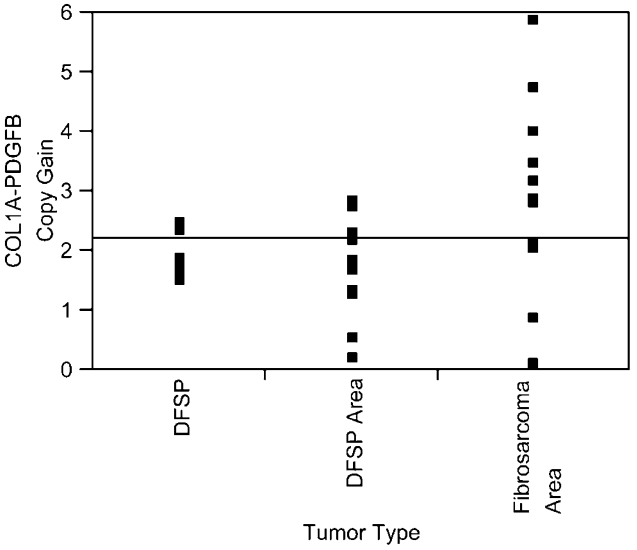

Figure 2 Comparison of *COL1A1-PDGFB* copy gains among classic dermatofibrosarcoma protuberans (left column) and the dermatofibrosarcoma protuberans and fibrosarcomatous areas of fibrosarcomatous dermatofibrosarcoma protuberans (right two columns).

analysis may obscure individual tumor oncogenic mechanisms. The use of fluorescence *in situ* hybridization allows for individual cases and individual areas to be compared, and counting signals allows for fine differentiation in trends and the exclusion of normal cells such as blood vessels, adipocytes or inflammatory cells by morphologic examination during the counting process.

No cases in our study set showed average *COL1A1-PDGFB* fusion gene copy gains above 5.85 copies. This relatively small gain is in contrast to other many other oncogenes that can be amplified at a much higher level. For example, *MYCN* is usually amplified 50- to 100-fold in neuroblastoma and *ERBB2* (*HER2*) can be amplified by up to 20 copies in breast carcinoma.[19] One explanation of this finding is that relatively low copy numbers of *COL1A1-PDGFB* can already provide a potent oncogenic stimulus to drive tumor proliferation in dermatofibrosarcoma protuberans and modest changes in the fusion gene copy number has a major effect in the fibrosarcomatous transformation. However, higher levels can lead to toxic cell signaling that ultimately results in apoptosis, therefore, negatively selecting these clones in a similar manner to what was shown in *MDM2* overexpressing mouse models.[20]

The observation that significant gains of the *COL1A1-PDGFB* fusion gene are not present in 40% of the study set implies that other oncogenic mechanisms must occur in the clonal evolution of fibrosarcomatous dermatofibrosarcoma protuberans. For example, both activating mutations in *PDGFB* or *PDGFRB* may lead to similar phenotypic effects. In addition to higher proliferation rates and gains of *TP53* mutations, Kiuru-Kuhlefelt *et al*[13] detected gains of whole or partial chromosomes 1 and 5 in their group of fibrosarcomatous dermatofibrosarcoma protuberans. Therefore, the amplification of the *COL1A1-PDGFB* fusion gene plays an important, but certainly not exclusive, role in the dedifferentiation of dermatofibrosarcoma protuberans into fibrosarcomatous dermatofibrosarcoma protuberans.

The genetic events that lead to the metastatic potential in fibrosarcomatous dermatofibrosarcoma protuberans are unknown. Previous retrospective clinicopathologic studies have shown an approximately 10% metastatic rate in fibrosarcomatous dermatofibrosarcoma protuberans, with lung and bone as common sites.[2,3] We analyzed a single case of fibrosarcomatous dermatofibrosarcoma protuberans that metastasized to a distant bone and the metastasis showed pure fibrosarcomatous morphology. The metastatic lesion possessed a slightly increased average *COL1A1-PDGFB* copy number gain over the fibrosarcomatous area, which in turn was similar to the average *COL1A1-PDGFB* copy number gain in the dermatofibrosarcoma protuberans area. This case demonstrates that the clonal selection for metastatic potential likely depends on multiple interrelated biologic factors and cannot be predicted by average *COL1A1-PDGFB* copy number gain. These data are consistent with data from epithelial tumors that show genetic instability quantitatively rises with tumor grade and aggressive behavior.[21]

The presence of 100% fibrosarcomatous morphology in the metastatic lesion with increased copy number gains of the *COL1A1-PDGFB* fusion gene highlights recent evidence that many superficial adult fibrosarcomas are indeed fibrosarcomatous dermatofibrosarcoma protuberans. In a case series by Sheng *et al*, four of six cases of superficial adult fibrosarcoma expressed the *COL1A1-PDGFB* fusion gene as detected by RT-PCR.[22] Importantly, genetic analysis of clinically aggressive fibrosarcomas may become clinically warranted since the presence of the *COL1A1-PDGFB* fusion gene carries potential therapeutic implications. Inhibitors of *PDGFB* such as imatinib mesylate have been shown to have activity against primary and metastatic dermatofibrosarcoma protuberans and fibrosarcomatous dermatofibrosarcoma protuberans in small trials.[23–25] In contrast, a small subset of dermatofibrosarcoma protuberans patients have shown transient or partial responses to imatinib.[25,26] The role of *PDGFB* activation in imatinib responsiveness has not been investigated, but it is possible that the subset of fibrosarcomatous dermatofibrosarcoma protuberans that operate with gains of *COL1A1-PDGFB* may be more susceptible to imatinib.[24] However, our data also clearly indicate that additional genetic factors such as gains of *TP53* mutations play an important role in tumor behavior.[2] Therefore, investigation of other oncogenic mechanisms in the *PDGFB-PDGFRB* signaling pathway is necessary.

Our results showed that copy number of *COL1A1-PDGFB* fusion gene in the classic dermatofibrosarcoma protuberans areas does not seem to be a major predisposing mechanism for fibrosarcomatous transformation. There was basically no difference in *COL1A1-PDGFB* fusion gene copy gain in the dermatofibrosarcoma protuberans areas of fibrosarcomatous dermatofibrosarcoma protuberans and classic dermatofibrosarcoma protuberans. Therefore, while fibrosarcomatous areas may contain increased copies of the fusion gene in a large subset of tumors, the value of fusion gene copy numbers in the dermatofibrosarcoma protuberans areas is not predictive of clinical behavior. These data emphasize the role that multiple genetic events must play in clonal evolution of fibrosarcomatous change.

In summary, genomic gains of *COL1A1-PDGFB* fusion gene were identified in 60% of dermatofibrosarcoma protuberans that clonally evolve into fibrosarcomatous dermatofibrosarcoma protuberans. The remaining cases of fibrosarcomatous dermatofibrosarcoma protuberans do not show genomic gains of this fusion gene, which suggests other alternate oncogenic mechanisms must exist in this transformation. In addition, copy number of *COL1A1-PDGFB* fusion gene in the classic dermatofibrosarcoma protuberans areas does not seem to be a major predisposing mechanism for fibrosarcomatous transformation.

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