

***TERT* promoter mutations are frequent in atypical fibroxanthomas and pleomorphic dermal sarcomas**

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Activating mutations in the *TERT* promoter leading to increased telomerase expression were recently identified in cutaneous melanoma and subsequently in many other types of cancer. These mutations lead to increased telomerase expression, allowing cells to proliferate continuously without entering apoptosis or senescence. Atypical fibroxanthomas and pleomorphic dermal sarcomas are genetically poorly understood tumors developing in the skin of older patients. Known genetic events in these tumors are mutations in *TP53* (atypical fibroxanthoma and pleomorphic dermal sarcoma) and *RAS* (pleomorphic dermal sarcoma) genes, often having a UV signature. We analyzed a cohort of 27 atypical fibroxanthomas and 34 pleomorphic dermal sarcomas for the presence of *TERT* promoter mutations by conventional Sanger sequencing. *TERT* promoter mutations were identified in 25 (93%) atypical fibroxanthomas and in 26 (76%) pleomorphic dermal sarcomas. Mutations were found to have a UV signature (C>T or CC>TT) and were largely identical to those detected in cutaneous melanoma. Our data show that *TERT* promoter mutations are the most frequent mutations in atypical fibroxanthomas and pleomorphic dermal sarcomas reported to date. The identified mutations confirm the pathogenetic role of UV exposure in both atypical fibroxanthomas and pleomorphic dermal sarcomas and suggest that telomere maintenance through increased expression of telomerase plays an important role in the pathogenesis of these tumors.

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Atypical fibroxanthomas and pleomorphic dermal sarcomas of the skin are rare mesenchymal tumors that typically arise in the skin of older patients and are genetically poorly characterized.

Atypical fibroxanthomas are rapidly growing exophytic tumors that occur in sun-damaged skin, primarily in the head and neck region of elderly patients.^{1–3} They are well-circumscribed tumors

occurring more frequently in males. Risk factors include UV exposure, irradiation, xeroderma pigmentosum, and organ transplantation.⁴ Histologically, they are usually composed of atypical spindled and pleomorphic tumor cells including tumor giant cells, and are centered within the dermis with limited extension into the subcutis. They show high mitotic activity including atypical mitotic figures.² However, they do not invade into the deep soft tissues, and despite increased proliferative activity, areas of tumor necrosis and lymphovascular and/or perineural invasion are not present. A diagnosis of atypical fibroxanthoma requires exclusion of other neoplasms, in particular, melanoma, squamous cell carcinoma, and leiomyosarcoma. Atypical

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fibroxanthomas generally have a good prognosis, and usually complete excision and regular follow-up are recommended.¹

The term 'pleomorphic dermal sarcoma' was introduced by Fletcher⁵ and describes tumors presenting with a similar morphology to atypical fibroxanthomas, but which in addition show extensive involvement of subcutis and/or invasion into deeper structures, areas of tumor necrosis, lymphovascular invasion, and perineural invasion. Pleomorphic dermal sarcomas exhibit more aggressive clinical behavior than atypical fibroxanthomas, and have the potential for local recurrence and metastasis.⁶ They are therefore categorized as tumors with low-grade malignant potential.⁶ The tumors now defined as pleomorphic dermal sarcomas have also been referred to as cutaneous undifferentiated pleomorphic sarcomas, and in the past as superficial malignant fibrous histiocytomas.⁷⁻⁹ There are currently no effective therapies for metastasized pleomorphic dermal sarcomas.

Distinguishing atypical fibroxanthoma from pleomorphic dermal sarcoma is not possible based on cell morphology alone, as they may show similar cytologic features. The criteria allowing the distinction of pleomorphic dermal sarcoma from atypical fibroxanthoma are: extensive infiltration of subcutis, or invasion into fascia or muscle; necrosis; and vascular or perineural invasion.^{2,5} Making the distinction between these tumors based solely on biopsy specimens should be avoided, as biopsies can be superficial or not show the deepest extent of tumor involvement. Although attempts have been made to identify immunohistochemical markers facilitating the distinction of atypical fibroxanthoma from pleomorphic dermal sarcoma (eg CD99 and LN-2 (refs. 10, 11)), none have proven reliable in routine practice.¹⁻³

Little is known of the genetic events leading to the development of atypical fibroxanthomas and pleomorphic dermal sarcomas. Previous small studies identified UV-signature mutations in *TP53* in atypical fibroxanthomas (7/10 (ref. 12) and 4/6 (ref. 13) cases) and pleomorphic dermal sarcomas (1/4 cases, diagnosed as 'malignant fibrous histiocytomas'¹³), as well as one *HRAS* mutation and one *KRAS* mutation in eight pleomorphic dermal sarcomas (diagnosed as 'malignant fibrous histiocytomas') analyzed.¹⁴ In another study, pleomorphic dermal sarcomas (diagnosed as 'undifferentiated pleomorphic sarcomas') were found to harbor more frequent DNA copy number alterations than atypical fibroxanthomas.¹⁵

Two recent studies in cutaneous melanomas identified novel recurrent mutations in the promoter region of *TERT*, coding for the catalytic subunit of the telomerase holoenzyme, in up to 71% of tumors.^{16,17} The mutations showed a characteristic UV signature (C>T and CC>TT).¹⁸ Functional studies found that these mutations lead to increased gene expression, most likely by creating ETS

transcription factor binding sites.^{16,17} A follow-up study screening a panel of different neoplasms identified *TERT* promoter mutations in a number of other common cancers, that is, in high frequencies in hepatocellular cancer, bladder cancer, and gliomas.¹⁹

In view of (a) the common occurrence of *TERT* promoter mutations with a UV signature in melanomas, (b) the strong association of atypical fibroxanthomas with UV exposure, and (c) the histologic similarities between atypical fibroxanthomas and pleomorphic dermal sarcomas, we investigated the presence of *TERT* promoter mutations in these tumors.

Materials and methods

Sample Selection

Atypical fibroxanthoma and pleomorphic dermal sarcoma tumor samples were obtained from the tissue archives of Dermatopathology Duisburg (17 atypical fibroxanthomas) and Dermatopathology Friedrichshafen (10 atypical fibroxanthomas, 9 pleomorphic dermal sarcomas), Germany, as well as from the Department of Pathology, Western General Hospital, The University of Edinburgh, Edinburgh, UK (25 pleomorphic dermal sarcomas, which were previously described by Miller *et al*⁶). The study was carried out in accordance with the guidelines set forth by the ethics committee of the University of Duisburg-Essen.

Histopathology and Immunohistochemistry

Histologic sections of all tumors were reviewed, and the diagnoses were confirmed by dermatopathologists (TB, TM, KGG, and JS). Analysis of available clinical and pathologic data was performed, including age, sex, site, size, depth, polyploid architecture, tumor mitotic rate, ulceration, necrosis, subcutis invasion, smooth muscle or fascia invasion, infiltrative or pushing border, lymphovascular invasion, and perineural invasion. All tumors were stained with a panel of immunohistochemical markers including: pan-cytokeratin (MNF116; 1/500, AE1/AE3; 1/50), CD31 (JC70A; 1/100) or CD34 (QBEnd-10; 1/50), S100 (polyclonal; 1/2000), desmin (D33; 1/100), smooth muscle actin (ASMA 1A4; 1/500), and melan-A (A103; 1/1000). All antibodies were obtained from DAKO Hamburg/Germany (Duisburg and Friedrichshafen cases). Stains in the cases from Edinburgh were performed as described previously.⁶

DNA Isolation

Sections, 10- μ m thick, were cut from formalin-fixed, paraffin-embedded tumor tissues. The sections were deparaffinized and tumor-bearing areas were manually macrodissected according to standard

procedures. Genomic DNA was isolated using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions.

Direct (Sanger) Sequencing

PCR amplification of a 474 bp region of the *TERT* promoter region was carried out applying the following primers: hTERT_F, 5'-ACGAACGTGGCCA GCGCAG-3' and hTERT_R, 5'-CTGGCGTCCCTGC ACCCTGG-3'. In cases where amplification of the large fragment failed, primers hTERT_short_F, 5'-CAGCGCTGCCTGAAACTC-3' and hTERT_short_R, 5'-GTCCTGCCCTTCACCTT-3', which amplify a 163 bp fragment, were applied as described previously.¹⁷ PCR products were purified with the QIAquick PCR Purification Kit (Qiagen) and used as templates for sequencing. The sequencing chromatogram files were examined and mutations were identified using Chromas software (version 2.01; University of Sussex, Brighton, UK) or Sequencher software (version 5.1; Gene Codes Corporation, Ann Arbor, MI, USA).

Results

Study Cohort

Sixty-one (27 atypical fibroxanthomas and 34 pleomorphic dermal sarcomas) tumors were analyzed, of which 59 were primary tumor samples and 2 were recurrent pleomorphic dermal sarcomas. Fifty-two patients were male and 9 were female. The median age at diagnosis was 82 (range 47–102) and 79 (range 65–93) years for patients with atypical fibroxanthomas, and 84 (range 47–102) years for patients with pleomorphic dermal sarcomas.

Clinical and Pathologic Features

Clinical and pathologic features are listed in Table 1. Representative images of an atypical fibroxanthoma and pleomorphic dermal sarcoma are shown in Figure 1. Tumors were generally negative for all listed immunohistochemical markers. Focal or patchy smooth muscle actin expression was seen in 11 (40%) atypical fibroxanthomas and 13 (39%) pleomorphic dermal sarcomas. As reported previously,⁶ 11 (32%) pleomorphic dermal sarcomas showed focal expression of CD31 and 1 pleomorphic dermal sarcoma exhibited limited aberrant expression of melan-A (S100 was negative).

TERT Promoter Mutation Analysis

Only samples showing unambiguous reads were included in the study. *TERT* promoter mutations were identified in 25 of 27 atypical fibroxanthomas (93%) and 26 of 34 pleomorphic dermal sarcomas

Table 1 Clinical and pathological features of atypical fibroxanthomas and pleomorphic dermal sarcomas

	All cases, N = 61	Atypical fibroxanthomas, N = 27	Pleomorphic dermal sarcomas, N = 34
<i>Age (years)</i>			
Median (range)	82 (47–102)	79 (65–93)	84 (47–102)
<i>Sex</i>			
Female	9	3	6
Male	52	24	28
<i>Site</i>			
Head	56	25	31
Neck	2	1	1
Arm	0	0	0
Not recorded	3	1	2
<i>Size</i>			
Median (range)	15.0 (4–60)	9.0 (4–30)	22.0 (6–60)
<i>Depth</i>			
Median (range)	10.0 (2–19)	5.0 (2–18)	12.0 (5–19)
<i>Tumor mitotic rate (per mm²)</i>			
Median (range)	19 (5–53)	20 (7–53)	19 (5–51)
<i>Ulceration</i>			
Absent	23	15	8
Present	38	12	26
<i>Necrosis</i>			
Absent	42	27	15
Present	19	0	19
<i>Invasion into subcutis</i>			
Absent	27	27	0
Present	34	0	34
<i>Invasion into fascia/skeletal muscle</i>			
Absent	37	27	10
Present	24	0	24
<i>Border</i>			
Infiltrating	17	0	17
Pushing	43	27	16
Not assessable ^a	1	0	1
<i>Lymphovascular invasion</i>			
Absent	52	27	25
Present	9	0	9
<i>Perineural invasion</i>			
Absent	52	27	25
Present	9	0	9
<i>Satellitosis</i>			
Absent	60	27	33
Present	1	0	1
<i>TERT promoter status</i>			
Wild type	10	2	8
Mutant	51	25	26

^aBorder not assessable as tumor extended to the excision margins.

(76%) (Table 2). Most of the mutations were identical to those described in cutaneous melanoma: chr. 5.1295228C>T (*n* = 19, 31%); chr. 5.1295228_

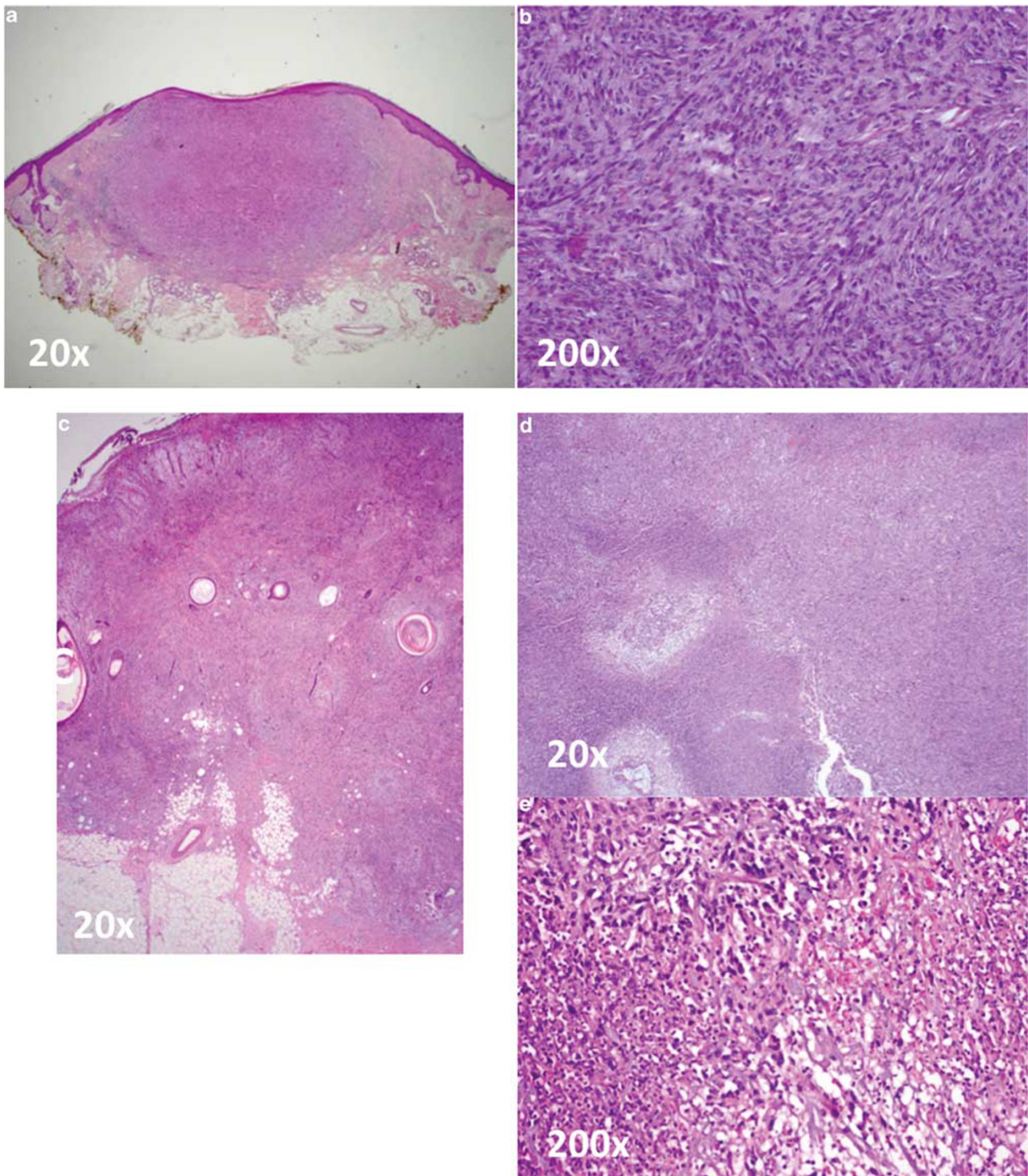


Figure 1 Examples of histologic features of atypical fibroxanthomas and pleomorphic dermal sarcomas. **(a and b)** Example of an atypical fibroxanthoma. **(a)** Relatively circumscribed, dermally centered tumor abutting the underlying subcutis. The overlying epidermis is thin and slightly invaginated (hematoxylin–eosin, $\times 20$). **(b)** The tumor is composed of atypical spindled and pleomorphic tumor cells (hematoxylin–eosin, $\times 200$). **(c–e)** Examples of pleomorphic dermal sarcomas. **(c)** Ulcerated, highly cellular tumor extensively infiltrating the dermis and subcutis (hematoxylin–eosin, $\times 20$). **(d)** Another highly cellular tumor exhibiting areas of necrosis (hematoxylin–eosin, $\times 20$). **(e)** High-power image of an area composed of highly atypical spindled and pleomorphic tumor cells and exhibiting areas of necrosis (hematoxylin–eosin, $\times 200$).

1295229 CC>TT ($n=9$, 15%); chr. 5.1295242_1295243CC>TT ($n=5$, 8%); and 1295250C>T ($n=20$, 33%). Mutations can alternatively be labeled according to their upstream location to the ATG initiation codon of *TERT*, which would be c. -124C>T, c. -124_125CC>TT, c. -138_139CC>TT, and c. -146C>T, respectively. For simplicity, we will refer to the mutations in the text using the last three digits of the chromosome location nomenclature,

Table 2 Distribution of *TERT* promoter mutations in atypical fibroxanthomas and pleomorphic dermal sarcomas

	Atypical fibroxanthomas		Pleomorphic dermal sarcomas		Total	
	N	%	n	%	n	%
<i>TERT</i> status						
Total	27	100	34	100	61	100
Mutant	25	93	26	76	51	84
Wild type	2	7	8	24	10	16
<i>Mutation distribution</i>						
228C>T	8	30	9	27	17	28
228C>T, 230C>T	1	4	0	0	1	2
228C>T, 250C>T	0	0	1	3	1	2
250C>T	6	22	11	32	17	28
250C>T, 253C>T	1	4	0	0	1	2
228CC>TT	6	22	2	6	8	13
228CC>TT, 242CC>TT, 250C>T	0	0	1	3	1	2
242CC>TT	3	11	1	3	4	7
228CCC>TTT	0	0	1	3	1	2

Mutations are annotated using the last three digits of their location chr. 5.1295xxx.

as 228C>T, 228CC>TT, 242CC>TT, and 250C>T, respectively (Figure 2).

In addition to these frequent mutations, a single 228CCC>TTT (chr. 5.1295228_1295229_1295230CCC>TTT) mutation was identified. Three tumors harbored either concurrent 228C>T and 230C>T (atypical fibroxanthoma), 228C>T and C250>T (pleomorphic dermal sarcoma), or 250C>T and 253C>T (atypical fibroxanthoma) mutations, and one tumor showed concurrent 228CC>TT, 242CC>TT, and 250C>T mutations (pleomorphic dermal sarcoma, Figure 2). All identified *TERT* promoter mutations had a UV signature (C>T and CC>TT).¹⁸ Most mutations were heterozygous; however, homozygous mutations affecting both alleles were also found (Figure 2).

Associations of Clinical and Pathologic Parameters with *TERT* Promoter Mutation Status

We explored associations of *TERT* promoter mutation status with each of the clinical and pathologic parameters listed in Table 1. The only feature that showed a statistically significant association with mutation status was necrosis, which was present in 11/26 (42%) and 8/8 (100%) of mutant and wild-type pleomorphic dermal sarcomas, respectively ($P=0.005$).

Discussion

TERT promoter mutations appear to be common genetic events in human cancers. Originally found in melanoma, they were later identified in a large variety of other human cancers.¹⁹ Our findings indicate that they are also common in atypical

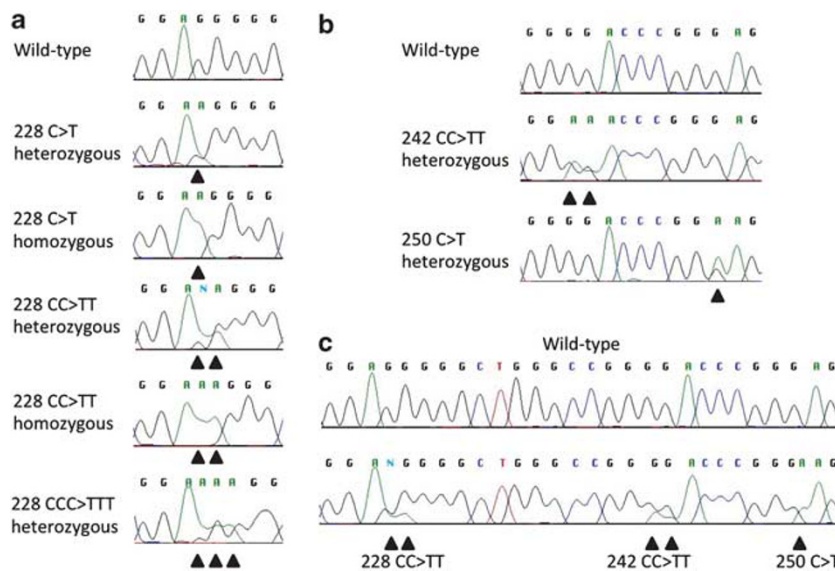


Figure 2 *TERT* promoter mutations identified in atypical fibroxanthomas and pleomorphic dermal sarcomas. (a) Mutations identified at or around the chr. 5.1295228 location. (Mutations in the figure are abbreviated using only the last three digits of the location of the first nucleotide mutated.) (b) Mutations identified in the chr. 5.1295242 and chr. 5.1295250 location (both abbreviated as mentioned before). (c) Example of one case that was identified harboring mutations at all mentioned sites.

fibroxanthomas and pleomorphic dermal sarcomas. The frequency of mutations (93% in atypical fibroxanthomas and 76% in pleomorphic dermal sarcomas) is even higher than those described in cutaneous melanoma (up to 71%).^{16,17} *TERT* promoter mutations were frequent in tumors arising from tissues with low self-renewal.¹⁹ Although conclusive experimental evidence to support the validity of this hypothesis in atypical fibroxanthomas and pleomorphic dermal sarcomas is lacking, it would appear to also apply to these tumors, which have been postulated to derive from fibroblastic/myofibroblastic cells.^{1,20–26}

UV exposure is considered to be a major risk factor for atypical fibroxanthoma, but its link to pleomorphic dermal sarcoma is less clear.^{9,12–14} In our cohort, the clinical presentation of both tumors was very similar, with tumors arising in elderly patients, on heavily sun-exposed areas (primarily head), with a strong male predominance (less hair protection), all of which support a role for UV exposure. The identification of *TP53* mutations with a UV signature is supportive of a pathogenetic role of UV exposure.^{12,13} All mutations identified in our study had a UV signature (C>T or CC>TT). However, both 228C>T and 250C>T mutations have also been found in tumor types for which a UV exposure link is unlikely, such as hepatocellular carcinoma and gliomas.¹⁹ In contrast, CC>TT mutations were not reported in the aforementioned tumors, but have been described in cutaneous melanoma.¹⁷ This is consistent with CC>TT mutations being virtually pathognomonic for UV exposure.^{18,27} We found high percentages of CC>TT mutations not only in atypical fibroxanthomas but also in pleomorphic dermal sarcomas. Nine (33%) atypical fibroxanthomas had CC>TT mutations (six 228CC>TT, three 242CC>TT) and five (15%) pleomorphic dermal sarcomas harbored CC>TT mutations (three 228CC>TT, two 242CC>TT, one 228CCC>TT—two of these found in one sample). These high mutation frequencies support UV exposure as an important pathogenetic factor in atypical fibroxanthoma and, to a lesser extent, pleomorphic dermal sarcoma.

Functional studies have shown that *TERT* promoter mutations lead to two- to fourfold increase in gene expression.^{16,17} The suggested mechanism is through the introduction of ETS transcription binding sites.^{16,17,19} In the present study, the mutations were found almost exclusively in the previously described *TERT* promoter mutation hotspots (54 of 56 mutations identified in 51 tumors, with all tumors harboring at least one hotspot mutation), even though there are multiple adjacent nucleotides that could acquire UV-induced C>T or CC>TT mutations (Figure 2). Although supporting functional data is not available for our cohort, the localization of the mutation to hotspots implies a high selection pressure for the identified mutations, resulting in overexpression of the holoenzyme telomerase.^{16,17} Telomerase expression in tumors is

critical for maintaining telomere length and chromosomal stability, allowing tumor cells to go through continuous rounds of cell division without becoming genetically unstable, and avoiding apoptosis or senescence.^{28,29}

In certain cancer types, Killela *et al*¹⁹ described alternative lengthening of telomeres associated with *DAXX* and *ATRX* mutations as a mechanism for telomere maintenance in tumors that lacked *TERT* promoter mutations. To our knowledge, alternative lengthening of telomeres has not been analyzed in atypical fibroxanthomas or pleomorphic dermal sarcomas. Although our findings imply that increased *TERT* expression is the predominant mechanism for telomere maintenance in these tumors, we cannot exclude the possibility that alternative lengthening of telomeres may have a role in the few cases that lack *TERT* promoter mutations.

Considerable debate remains as to the relationship between atypical fibroxanthomas and pleomorphic dermal sarcomas. Atypical fibroxanthoma was long regarded as a superficial variant of pleomorphic dermal sarcoma (then diagnosed as malignant fibrous histiocytoma). The genetic data presented by Mihic-Probst *et al*¹⁵ suggests a pathogenetic link. They found that atypical fibroxanthomas and pleomorphic dermal sarcomas (for which they used the term ‘undifferentiated pleomorphic sarcomas’) shared many common copy number alterations, although higher numbers of alterations were detected in the latter.¹⁵ However, the relationship (if any exists) between the two tumors remains to be fully elucidated.

The genetic underpinnings of atypical fibroxanthoma and pleomorphic dermal sarcoma are poorly understood. To date, only *TP53* mutations in 67–70%^{12,13} of atypical fibroxanthomas and 25% of pleomorphic dermal sarcomas (diagnosed as superficial malignant fibrous histiocytomas¹³) and *RAS* mutations in 25% of pleomorphic dermal sarcomas (diagnosed as malignant fibrous histiocytoma¹⁴) have been described. The mutations in the *TERT* promoter described in the present study constitute the most prevalent mutation identified to date in both tumors.

In summary, our data highlight that *TERT* promoter mutations are frequent in atypical fibroxanthomas and pleomorphic dermal sarcomas, and represent the most common mutation described in these tumors to date. The considerable number of CC>TT mutations found further suggests a role for UV induction in the pathogenesis of atypical fibroxanthomas and pleomorphic dermal sarcomas. Future studies will be required to determine whether *TERT* promoter mutation status could be of prognostic or therapeutic relevance.

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Disclosure/conflict of interest

DS is on the advisory board or has received honoraria from Roche, Genetech, Novartis, Amgen, GSK, BMS, Boehringer Ingelheim, and Merck. LZ has received honoraria from Roche, Bristol-Meyers Squibb, and Amgen, and travel support from Merck Sharp & Dohme and Bristol-Meyers Squibb. BS received travel support from Bristol-Meyers Squibb. All the other authors declare no conflict of interest.

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