

A subset of cranial fasciitis is associated with dysregulation of the Wnt/ β -catenin pathway

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Cranial fasciitis, an unusual fibroproliferative lesion that occurs in the scalp of infants, is considered a posttraumatic reactive process similar to nodular fasciitis. Its pathobiology has not been investigated. Over the last 15 years, we diagnosed cranial fasciitis in six children; in one case, the lesion recurred after 4 years. This lesion and two others showed aberrant, diffuse nuclear reactivity for β -catenin. One of the lesions with aberrant nuclear β -catenin occurred in a child with a history of familial adenomatous polyposis (FAP) and a germline frameshift adenomatous polyposis coli (*APC*) mutation, c.878delG. The other *APC* allele in this tumor showed an acquired nonsense mutation, c.4132C→T. Both these mutations lead to translation of a truncated APC protein. The other two cases of cranial fasciitis with aberrant nuclear β -catenin occurred sporadically. One of these showed a point mutation, c.122C→T, in exon 3 of *CTNNB1*. This mutation causes replacement of threonine with isoleucine at codon 41, leading to loss of a phosphorylation site in the β -catenin protein. The third case with nuclear β -catenin staining was the single one that showed recurrence. This tumor did not show mutations in exon 3 of *CTNNB1* or in exons 8/9/16 of *APC*. The results of this small study indicate a dysregulation of the Wnt/ β -catenin pathway in a subset of cranial fasciitis, suggesting that this subset is pathobiologically related to desmoid fibromatoses rather than to nodular fasciitis. Occasional cases of cranial fasciitis may be associated with FAP and serve as an early indicator of this disease, information that would be important in the early diagnosis of FAP in patients without a family history of polyposis.

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Cranial fasciitis is an uncommon benign fibroblastic proliferation that histologically resembles nodular fasciitis, but occurs preferentially in the scalp of younger children, usually infants. It apparently occurs sporadically, probably secondary to trauma and is not known to be associated with any syndrome. Cranial fasciitis almost never recurs, despite incomplete excision.¹

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder that occurs because of loss of function mutations of the adenomatous

polyposis coli (*APC*) gene. In addition to intestinal polyps and carcinomas, patients with FAP may develop the fibroblastic proliferative lesions, desmoid fibromatosis and Gardner fibroma. An association between FAP and cranial fasciitis has not previously been described. In this article, we show that a subset of cranial fasciitis cases has an aberrant Wnt/ β -catenin signaling pathway and that cranial fasciitis may occur in association with FAP.

Materials and methods

We retrieved and reviewed hematoxylin and eosin-stained sections of seven cases of cranial fasciitis diagnosed in the last 15 years at Children's Medical Center of Dallas. In addition, we studied nine cases of nodular fasciitis diagnosed in the same period.

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β -Catenin Immunohistochemistry

One representative block from each case of cranial fasciitis and nodular fasciitis was selected and 4 μ m thick sections were cut. Immunoperoxidase staining was performed on a BenchMarkXT automated immunostainer, using the UltraVIEW system with horseradish peroxidase and diaminobenzidine (DAB) chromogen (Ventana Medical Systems, Tucson, AZ, USA). Heat-induced epitope retrieval was used and the antibody to β -catenin (Zymed Laboratories, Invitrogen Immunodetection, South San Francisco, CA, USA) was used at a dilution of 1:3200.

APC (N Terminus) Immunohistochemistry

One representative block from each case of cranial fasciitis was selected and 4- μ m thick sections were cut. Immunoperoxidase staining was performed on a DiscoveryXT-automated immunostainer, using the ChromoMap system with horseradish peroxidase and DAB chromogen (Ventana Medical Systems). Heat-induced epitope retrieval was used and the antibody to APC (N terminus) (ab16794; Abcam, Cambridge, MA, USA) was used at a dilution of 1:20.

CTNNB1 and APC Gene Sequencing

The exon 3 of *CTNNB1*, the gene for β -catenin, contains the region for glycogen synthase kinase 3 β (GSK3 β) phosphorylation. This exon was amplified using previously published primer pairs: F: 5'-ATGGAACCAGACAGAAAAGC-3' and R: 5'-GCTA-CTTGTCTTGAGTGAAG-3'.² The exon 16 of *APC* contains the mutation cluster region. This region and the exons 8 and 9 were amplified using the following set of primers: F: 5'-TGCCA CTTGCAAAGTTTCTTC-3' and R: 5'-GGCTGGCTTT TTTGCTTTAC-3' for exon 16; F: 5'-CGCCAATCGTA CTGGAGGT-3' and R: 5'-TGGTACTGAATGCTTCTG GAAA-3' for exon 8; F: 5'-CCATTCTGCAGTTTAA TGCTCA-3' and R: 5'-TCCCAAATGCTGGGATT AC-3' for exon 9. Genomic DNA was extracted from formalin-fixed paraffin-embedded tissue using the QIAamp DNA Mini Kit (Qiagen, Valencia, CA, USA) using the manufacturer's protocol. PCR amplification was performed in a 25- μ l volume containing 1.5U Takara Hot Start Taq polymerase, 4mM MgCl₂ and 200 μ M dNTP (OmniMix HS; Cepheid, Sunnyvale, CA, USA), and 1 μ M of each primer pair. All PCR products were purified with QIAquick PCR purification kit (Qiagen) before sequencing. Automated sequencing of purified PCR products was performed in both directions, at the DNA Sequencing Core facility at UT Southwestern Medical Center (<http://www8.utsouthwestern.edu/utsw/cda/dept108278/files/111118.html>).

The study was approved by the institutional review board of UT Southwestern Medical Center, Dallas, TX, USA.

Table 1 Demographic and pathological characteristics of the cases of cranial fasciitis

Case ^a	Age at diagnosis	Sex	β -Catenin IHC
C1	1 year	M	Cytoplasmic
C2	1 year	F	Cytoplasmic
C3 ^b	4 months	F	Nuclear
C4	5 years 3 months	F	Cytoplasmic
C5 ^a	2 years 2 months	M	Nuclear
C6 ^a	6 years 4 months	M	Nuclear
C7 ^c	3 years 4 months	M	Nuclear

F, female; IHC, immunohistochemistry; M, male.

^aThe cases C5 (primary tumor) and C6 (recurrence) occurred in the same patient. No mutations were found in exon 3 of *CTNNB1* or exons 8/9/16 of *APC*.

^bThis tumor had an oncogenic missense mutation, c.122CT, of *CTNNB1*.

^cThis tumor had the germline frameshift mutation, c.878delG, and an acquired nonsense mutation, c.4132CT, of *APC*.

Results

The seven cases of cranial fasciitis occurred in six patients, with one case recurring after 4 years. Of the six patients, three were boys and three girls; the age at initial presentation ranged from 4 months to 5.3 years. One patient was from a family with FAP and carried a germline frameshift *APC* mutation, c.878delG. This child did not have the gastrointestinal manifestations of FAP and his cranial lesion was clinically thought to be an osteoma. All other cases, including the one with recurrence, were sporadic (Table 1).

All cases had the characteristic histomorphologic features of cranial fasciitis (Figure 1). All tumors were composed of short fascicles of spindle cells in a background of myxoid and loose collagenous stroma. There were numerous scattered extravasated red cells and a few lymphocytes, but no lymphoid aggregates were noted in any case. Prominent dilated blood vessels were seen in one case (no. C3; Table 1). Focal keloidal collagen, osseous metaplasia and erosion of the outer table of the cranial vault were present in many lesions.

Immunohistochemistry for β -catenin demonstrated cytoplasmic staining in three cases of cranial fasciitis and nuclear staining in the remaining four (Figure 2). These four lesions occurred in three children and included the child with FAP and the only patient with recurrent disease (Table 1). All nine cases of nodular fasciitis showed only cytoplasmic staining for β -catenin.

Immunohistochemistry for the N terminus of APC demonstrated predominantly cytoplasmic staining in all cases of cranial fasciitis (Figure 3).

The cranial fasciitis that occurred in the child with FAP (no. C7; Table 1) had the germline *APC* mutation, c.878delG. This mutation leads to a premature stop codon at amino acid 304, resulting in a truncated APC protein. The other *APC* allele in

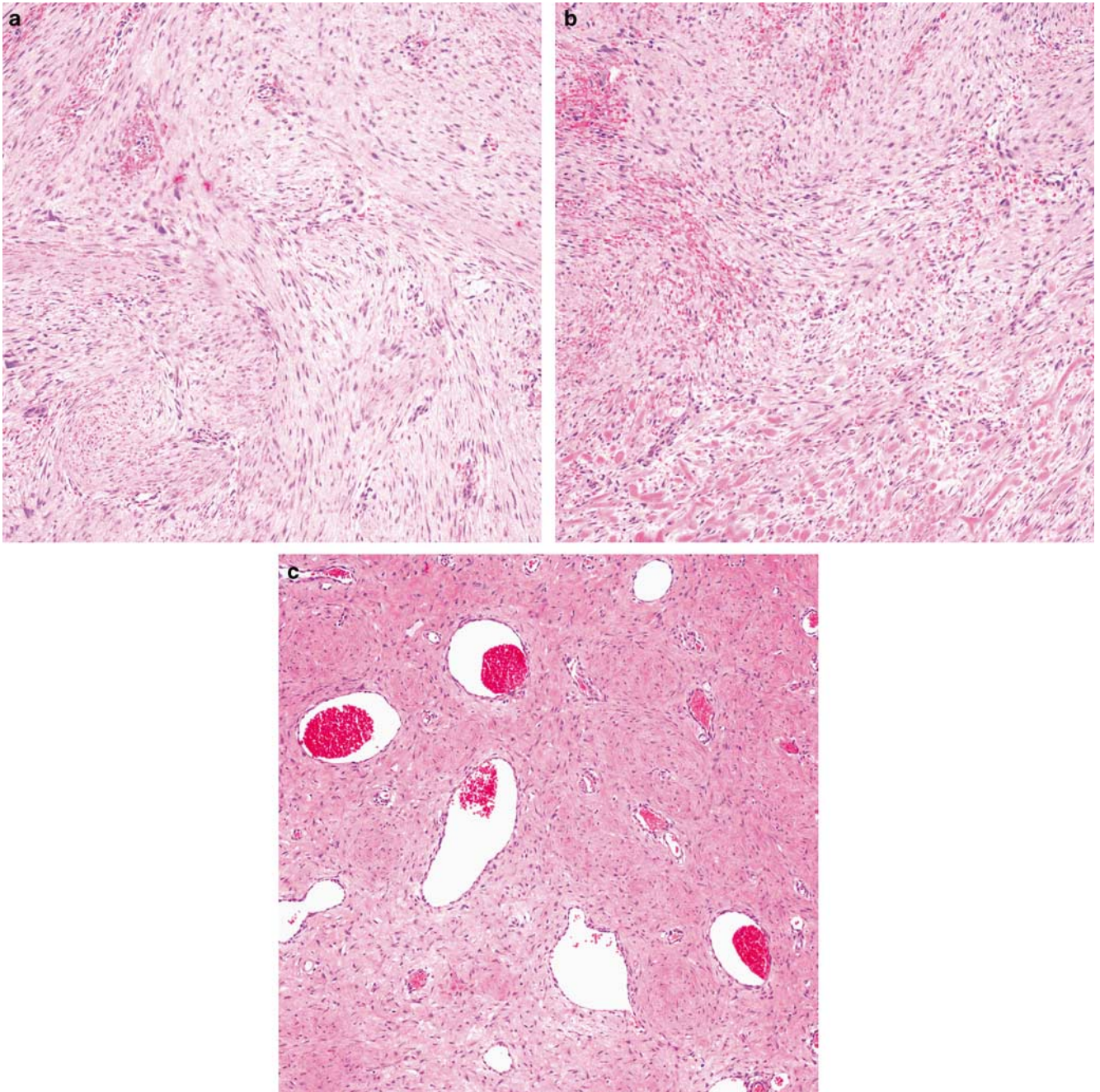


Figure 1 All cases of cranial fasciitis had the characteristic histopathologic features of short fascicles of fibroblasts and myofibroblasts embedded in a variably collagenous and myxoid stromal background, with many extravasated red blood cells (a). Occasional foci of keloidal collagen were seen (b). One case (no. C3; Table 1) showed prominent dilated vessels, but was otherwise morphologically and clinically consistent with cranial fasciitis (c) (hematoxylin and eosin, $\times 200$).

this tumor showed an acquired nonsense mutation, c.4132C \rightarrow T that leads to a premature stop codon at amino acid 1378, again resulting in a truncated APC protein (Figures 4a and b). The second case with nuclear β -catenin (no. C3; Table 1) had an oncogenic missense mutation of *CTNNB1*, the gene-encoding β -catenin (Figure 4c). This c.122C \rightarrow T mutation causes replacement of threonine with isoleucine at codon 41, thereby leading to loss of a GSK3 β phosphorylation site in the β -catenin protein. The

third case with nuclear β -catenin staining was the only one that recurred (nos. C5 and C6; Table 1). This case did not show mutations in exon 3 of *CTNNB1* or exons 8/9/16 of *APC*.

Discussion

Cranial fasciitis was first described in 1980 by Lauer and Enzinger.¹ It is an uncommon fibroblastic/

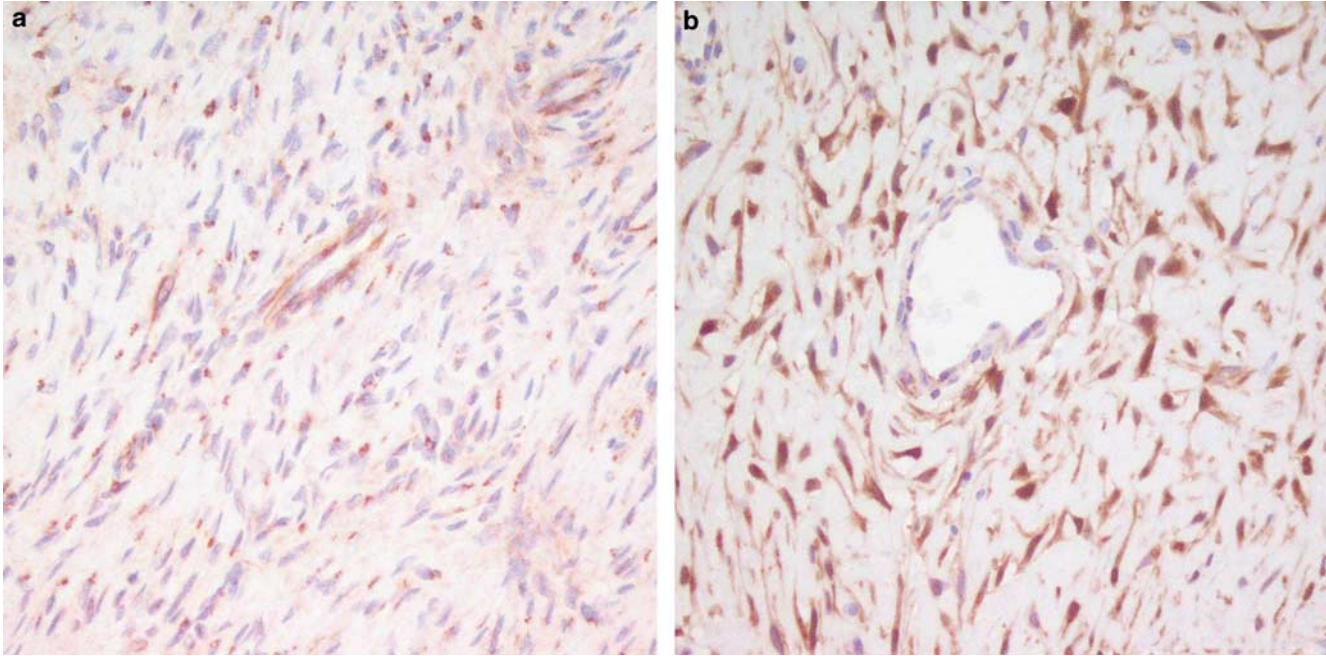


Figure 2 Three cases of cranial fasciitis demonstrated cytoplasmic reactivity (a) and four showed nuclear reactivity (b) for β -catenin (immunoperoxidase, $\times 400$).

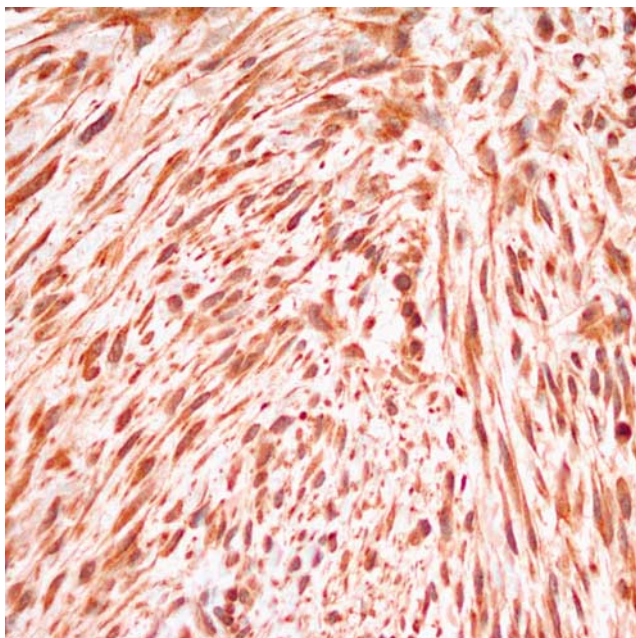


Figure 3 All cases of cranial fasciitis demonstrated predominantly cytoplasmic reactivity for N terminus of APC. This photomicrograph is from the case (no. C5; Table 1) with aberrant nuclear β -catenin localization and no mutations in exon 3 of *CTNNB1* or exons 8/9/16 of *APC* (immunoperoxidase, $\times 400$).

myofibroblastic proliferation that mimics nodular fasciitis histologically and in its clinical presentation as a rapidly growing soft tissue mass. However, it differs from nodular fasciitis in that it occurs predominantly in the soft tissues of the scalp of younger children, especially infants. Cranial fasciitis often erodes through the outer table of the

adjacent cranial vault, sometimes eroding through the inner table and involving the meninges.³ Rarely, cranial fasciitis may arise from the dura and be exclusively intracranial.^{4,5}

Pathophysiologically, cranial fasciitis is considered a benign process, probably of reactive nature, often occurring at sites of previous trauma.⁶ A parasagittal cranial fasciitis was reported to develop in an 11-year-old child, 4 years after cranial irradiation for medulloblastoma.⁷ The presumption of a reactive process is reflected in the name 'congenital reactive myofibroblastic tumor' used by Pollack *et al.*⁸ In the original series of nine cases reported by Lauer and Enzinger,¹ no recurrences or aggressive behavior were noted. Subsequent reports have confirmed the benign nature of these lesions. Even a presumed residual lesion after incomplete resection was reported to undergo spontaneous regression.⁸

β -catenin is a cytoplasmic protein normally located adjacent to the cell membranes, where it interacts with and stabilizes the transmembrane E-cadherin, thereby participating in cell-cell adhesion. β -catenin also functions as a transcription factor in the Wnt-signaling pathway. In the presence of Wnt signal, during vertebrate embryogenesis, the unphosphorylated β -catenin accumulates in the cytoplasm and translocates to the nucleus where it functions as a cofactor for the transcription factors belonging to the T-cell factor/lymphoid enhancing factor family. In the absence of Wnt signal, in the normal post-embryogenesis period, the cytoplasmic β -catenin is phosphorylated and degraded via a process requiring the ' β -catenin destruction complex' composed of APC, axin and GSK3 β . Mutations

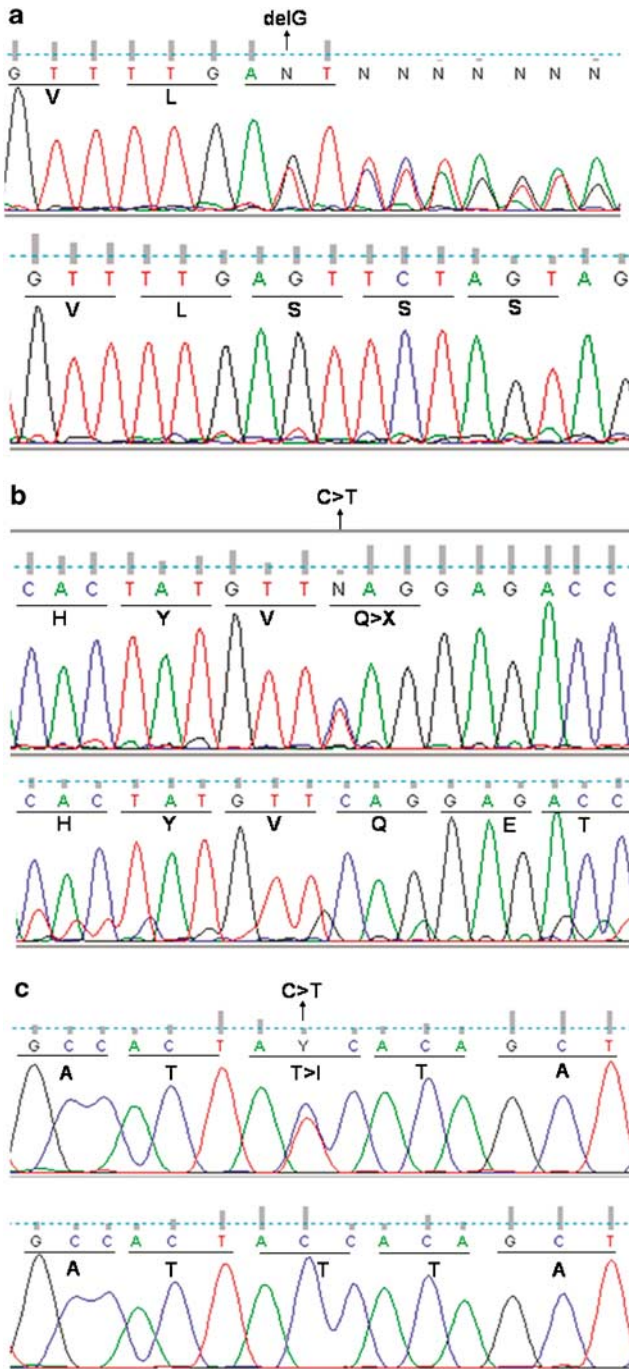


Figure 4 In these sequencing chromatograms, the top panel is from cranial fasciitis and the bottom panel is the corresponding control sequence. The lesion that occurred in the child with FAP (no. C7; Table 1) had the germline frameshift *APC* mutation, c.878delG (a) and an acquired nonsense *APC* mutation, c.4132C→T (b). Both these mutations lead to production of a truncated *APC* protein. One of the sporadic cases of cranial fasciitis with nuclear β -catenin (no. C3; Table 1) had an oncogenic missense *CTNNB1* mutation, c.122C→T (c). This mutation causes replacement of threonine with isoleucine at codon 41, thereby leading to loss of a GSK3 β phosphorylation site in the β -catenin protein. A, alanine; E, glutamate; H, histidine; I, isoleucine; L, leucine; Q, glutamine; S, serine; T, threonine; V, valine; X, stop; Y, tyrosine.

in the genes encoding the proteins involved in Wnt-signaling and β -catenin degradation may lead to persistence of β -catenin in the cytoplasm and subsequent translocation to the nucleus, where it then functions to activate the genes involved in cell proliferation and/or inhibition of apoptosis.^{9,10} Such mutations occur in numerous human epithelial cancers.¹¹ The germline *APC* mutations are responsible for FAP and related syndromes that predispose to colonic adenomas and carcinomas.¹² In addition, the translocation of β -catenin away from E-cadherin may lead to reduced cell–cell adhesion and promote cancer metastasis.^{13,14}

Immunohistochemical staining for β -catenin has been used as a surrogate marker for the integrity of the canonical Wnt-signaling and β -catenin degradation pathways. Normally, immunohistochemical staining for β -catenin shows a membranous pattern of staining in epithelial cells. However, if the Wnt-signaling pathway is activated or the β -catenin degradation pathway is inactivated, β -catenin accumulates in the cytoplasm and/or the nucleus.^{15,16}

In contrast to the purely membranous localization in normal epithelial cells, β -catenin staining in mesenchymal cells is limited to the cytoplasm and/or the cell membranes.¹⁷ β -catenin may be involved in normal wound healing and abnormal proliferations of fibroblasts.¹⁸ Among mesenchymal tumors, aberrant localization of β -catenin has been described in solitary fibrous tumors, osteosarcomas, malignant phyllodes tumors, liposarcomas, malignant fibrous histiocytomas, synovial sarcomas, malignant peripheral nerve sheath tumors and myxofibrosarcomas,^{19–24} but the dysregulation and nuclear localization of β -catenin is most strongly associated with desmoid fibromatoses and Gardner fibromas, both sporadic and those associated with FAP and its variant syndromes.^{17,25–29}

By immunohistochemistry, β -catenin is seen in the cytoplasm of the lesional cells of nodular fasciitis, with no accumulation in the nucleus.^{30,31} Similar to the previous results, all of our nine cases of nodular fasciitis showed only cytoplasmic staining for β -catenin. Results of immunohistochemical staining for β -catenin have not previously been reported for cranial fasciitis. In our small series, cranial fasciitis from three of six patients showed aberrant nuclear localization of β -catenin. In addition, the only recurrent case of cranial fasciitis in our series showed nuclear accumulation in both the primary lesion and in the recurrence.

One of our cases of cranial fasciitis with nuclear β -catenin occurred in a child from a family with FAP and known to carry a germline *APC* mutation. The tumor tissue in this case showed the germline *APC* mutation, c.878delG, as well as an acquired nonsense mutation, c.4132C→T. Both these mutations lead to the production of a truncated *APC* protein. The nuclear localization of β -catenin in this case confirms that the acquired somatic *APC* mutation occurred in the other allele, and implicates the

Wnt/ β -catenin pathway in the development of this lesion. An association between cranial fasciitis and FAP has not been previously reported. However, de Silva *et al*³² did report the occurrence of a 'cranial desmoid tumor' showing homozygous *APC* inactivation in a 2-year-old girl with a family history of FAP. Interestingly, the authors stated that the lesion had 'some features of cranial fasciitis, including myxoid change and occasional extravasated erythrocytes'. Our case had the classical histological features of cranial fasciitis and did not resemble desmoid fibromatosis.

All of our other cases of cranial fasciitis were apparently sporadic and were not associated with a known family history of FAP or any other syndrome. Of these, two cases showed aberrant nuclear localization of β -catenin. In one of these cases, we found a point mutation, c.122C→T, of *CTNNB1*, the gene-encoding β -catenin. This missense mutation leads to insertion of isoleucine in place of threonine at codon 41. This change causes the loss of a phosphorylation target site for GSK3 β , a part of the β -catenin destruction complex. This mutation, which was found to be highly oncogenic in a rat model of chemically induced colonic tumors,³³ has not been described in desmoid fibromatosis or other fibroproliferative tumors, but has been reported in adamantinomatous craniopharyngiomas.^{34,35}

The third case of cranial fasciitis with aberrant nuclear β -catenin was the only one that recurred after 4 years. Both the primary and the recurrent tumors showed nuclear β -catenin. This case did not show mutations in exon 3 of *CTNNB1* or exons 8/9/16 of *APC*. A mutation elsewhere in *CTNNB1* or in *APC* or other genes involved in the turnover of β -catenin may be responsible for the aberrant nuclear localization of β -catenin in this case. Of note, immunohistochemistry for the N terminus of *APC* showed positive staining.

In summary, we have shown that a subset of cases of cranial fasciitis is associated with molecular alterations leading to aberrant persistence and nuclear localization of β -catenin. We suggest that this subset of cranial fasciitis has clinical and molecular features similar to desmoid fibromatosis and Gardner fibroma, in that some cases occur in association with FAP and show loss-of-function *APC* mutations, whereas other cases occur sporadically and show either gain-of-function *CTNNB1* mutations or other yet unidentified mutations. In fact, it is possible that the cases of cranial fasciitis with aberrant nuclear localization of β -catenin are actually early desmoid fibromatoses. On the other hand, the cases of cranial fasciitis without aberrant nuclear localization of β -catenin may arise because of mutations in the Wnt/ β -catenin pathway downstream of β -catenin. In any case, immunohistochemistry for β -catenin should be performed in all cases with the clinicopathologic features of cranial fasciitis. As cranial fasciitis occurs in younger children, especially infants, nuclear localization of β -catenin,

especially when accompanied by inactivating *APC* mutations, should alert the clinician to the possibility of future occurrence of colonic adenomas and adenocarcinomas. It is pertinent to note that the patients with FAP do not develop colonic adenomas and adenocarcinomas until adolescence or early adulthood and that 30–40% of FAP result from new germline *APC* mutations and, therefore, without a family history of the disease.³⁶

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Disclosure/conflict of interest

None.

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