Cancer Genetics 205 (2012) 410–413

Cancer Genetics

BRIEF COMMUNICATION

Molecular genetic characterization of the 11q13 breakpoint in a desmoplastic fibroma of bone

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Desmoplastic fibroma (DFB) is a benign primary bone tumor that usually occurs in adolescents and young adults. The genetic information on DFB is very limited. We here present cytogenetic, fluorescence in situ hybridization and single nucleotide polymorphism array findings in a case that had a rearrangement involving chromosomes 11 and 19 at G-banding analysis. The results showed that the breakpoint in 11q was different from that in desmoplastic fibroblastomas, and a segment containing five genes was hemizygously deleted from 11q13.

Keywords Desmoplastic fibroma, desmoplastic fibroblastoma, FISH, SNP array, 11q13

Desmoplastic fibroma of bone (DFB) is a rare, benign primary skeletal tumor first described by Jaffe in 1958 (1). It occurs typically in adolescents and young adults. Long bones and the mandible are most commonly affected, but the pelvis may also be involved (2,3). Tumors can be up to 20 cm in diameter and have a grey-white, fibrous, solid appearance. The morphology of DFB is similar to that of a desmoid tumor of soft tissue (DT; also known as desmoid-type fibromatoses), with spindle-shaped fibroblasts, dense collagen matrix, rare mitotic figures, and variable cellularity as well as displaying an infiltrative growth pattern. Ultrastructural and immunohistochemical studies have suggested a myofibroblastic differentiation. In addition, the clinical features of DFB are similar to those of DT, with frequent local recurrences. Malignant transformation, and secondary malignancies at the same site, have been reported in rare cases (4–6). DFB has not been extensively analyzed at the genetic level. A combined cytogenetic and fluorescence in situ hybridization (FISH) study of three cases consistently revealed a normal karyotype after short-term culturing, while interphase FISH indicated the presence of trisomy 8 and 20 in one of them (7). Hauben et al. (8) investigated six cases with regard to mutations in the β-catenin (*CTNNB1*) gene; all were negative. Finally, Min et al. (6) used array comparative genomic hybridization (CGH) and identified losses at 1p, 3p, 6p, 10p, 18q, and 22q and gains at 7p and 9q in different areas of a tumor with malignant transformation. Thus, no consistent aberrations have been detected and the genetic overlap with DT is limited thus far.

In the present study, we report the finding of an abnormal karyotype in one case of DFB. As the karyotype suggested a relationship with another benign fibroblastic soft tissue lesion—desmoplastic fibroblastoma—further analyses using single nucleotide polymorphism (SNP) array and FISH were performed.

Materials and methods

A 20-year-old woman presented with a tumor in her right proximal femur. After excision at a local hospital, the tumor recurred, and she was referred to an orthopedic tumor center. After renewed excision, the patient has remained disease-free for more than 10 years. Histopathologic examination revealed a benign fibroblastic tumor, compatible with DFB.

Received April 5, 2012; received in revised form May 2, 2012; accepted May 2, 2012.

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doi:10.1016/j.cancergen.2012.05.002

Table 1 Deliniation of 11q13 breakpoint by FISH

BAC/fosmids probes	Position (Mb)[a]	FISH results
RP11-485A12	chr11:57,562,610-57,728,143	der(11)
RP11-947H5	chr11:58,748,029-58,916,998	der(11)
RP11-697E9	chr11:61,111,690-61,315,975	der(11)
RP11-143B16	chr11:65,351,387-65,517,724	der(11)
RP11-692F22	chr11:65,388,906-65,562,696	der(11)
RP11-506O3	chr11:65,641,027-65,815,317	der(11)
RP11-142G8	chr11:65,876,916-66,035,381	der(11)
RP11-669D23	chr11:66,104,949-66,305,399	der(11)
G248P87552D7	chr11:66,302,883-66,345,222	deleted
G248P84600D3	chr11:66,343,615-66,386,333	der(19)
G248P85430G4	chr11:66,386,802-66,426,096	der(19)
RP11-15L8	chr11:66,379,948-66,562,716	der(19)

[a] Base pair positions according to the NCBI build 36 (hg18).

Cytogenetic and FISH analyses

A fresh tumor sample was obtained for chromosome banding analysis and additional molecular studies. Chromosome banding and FISH analyses (9,10) were performed as described. Bacterial artificial chromosomes (BAC) and fosmid probes for FISH analysis (Table 1) were selected using the UCSC database (http://genome.ucsc.edu, released March 2006).

SNP array analysis

To identify genomic gains or deletions, the tumor was analyzed by SNP array with the Illumina Human Omni-Quad version 1.0 BeadChip, according to standard protocols supplied by the manufacturer (Illumina, San Diego, CA). The position of the SNPs was based on the UCSC hg/18NCBI Build 36 sequence assembly. Imbalances were identified by visual inspection. Constitutional copy number polymorphisms were excluded based on comparison with the Database of Genomic Variants (http://projects.tcag.ca/cgibin/variation/gbrowse/hg18/) (11).

Results

G-banding analysis of metaphase spreads from short-term cultured cells revealed the following karyotype: 46, XX,del(11)(q13q23),der(19)t(11;19)(q13;p13)del(11)(q23) (Figure 1A). Using the probes listed in Table 1, a breakpoint in 11q13 was mapped between BAC probes RP11-669D23 (chr11:66,104,949-66,305,399), which showed a weaker signal on the derivative chromosome 11 than on the normal homologue, and RP11-15L8 (chr11:66,379,948-66,562,716), which gave signals on the normal chromosome 11 and on the derivative chromosome 19 (Figure 1B). Further FISH with fosmid probes showed that the region recognized by G248P87552D7 (chr11:66,302,883-66,345,222) was deleted from the derivative chromosome 11 and that G248P84600D3 (chr11:66,343,615-66,386,333) mapped to the derivative chromosome 19 (Figure1C) To search for a cryptic rearrangement of the breakpoint region in 11q13 previously identified in desmoplastic fibroblastoma (13), FISH was performed with BAC probes RP11-143B16 and RP11-692F22; no rearrangement was found (Figure 1D). Based on the FISH results, the karyotype was reinterpreted as 46,XX,del(11)(q13q23),der(19)ins(19;11)(p13;q13q23). SNP array analysis showed a ~230 kb hemizygous deletion in 11q13 (chr11:66,137,069-66,366,299), in agreement with the FISH results (Figure 1E). Thus, the insertion of material from chromosome 11 into chromosome 19 was associated with the loss of five genes (*RBM14*, *RBM4*, *RBM4B*, *SPTBN2*, and *C11orf80*) from 11q13.

Discussion

The present case of DFB is the first with an abnormal karyotype. As the only clonal rearrangement, we found an exchange between chromosome arms 11q and 19p. Bearing in mind that some soft tissue lesions, notably desmoplastic fibroblastoma (12), also have characteristic chromosome rearrangements of chromosome band 11q12-13, we decided to investigate whether the breakpoint in the DFB coincided with those detected in desmoplastic fibroblastoma. Using FISH and the SNP array, we could demonstrate that the 11q13 breakpoint in the DFB is located approximately 800 kb telomeric to the breakpoints in desmoplastic fibroblastomas and, furthermore, that the cytogenetic exchange in the DFB was associated with a ~230 kb deletion in 11q13, a phenomenon not observed in desmoplastic fibroblastomas. Thus, our results do not indicate a shared pathogenetic mechanism in these two tumor types. Previous cytogenetic analysis of three cases did not reveal any clonal aberrations (7); however, a normal karyotype could be due to outgrowth of stromal cells. The only previous array-based analysis of genomic imbalances did not detect any losses at 11q (6); however, that study was performed using a low-resolution array with, on average, 1 Mb between probes. Thus, smaller deletions, as in our case, could easily have been missed. Furthermore, the case analyzed by Min et al. was highly unusual in the sense that it showed malignant transformation (6).

The chromosome aberration detected in the present case could indicate that rearrangement of one or more genes in 11q and/or 19p is of pathogenetic significance. The concomitant hemizygous loss of an ~230 kb genomic region in 11q, containing the genes *RBM14*, *RBM4*, *RBM4B*, *SPTBN2*, and *C11orf80*, could also point to a tumor suppressor role for one of these genes. None of them has been implicated in tumorigenesis previously, but the three *RBM* genes are of potential interest. *RBM14* encodes the RNA-binding motif protein 14, which exists in two isoforms. Isoform 1 may function as a nuclear receptor coactivator, whereas isoform 2 functions as a transcriptional repressor (13). *RBM4* and *RBM4B* may have a role in micro-RNA-mediated gene regulation; they also have a role in the selection of alternative splice sites during pre-mRNA processing (14).