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BRIEF COMMUNICATION

Chromosome Band 1q21 Is Recurrently Gained in Desmoid Tumors

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DNA sequence copy number changes were studied by comparative genomic hybridization (CGH) in 28 desmoid tumors. Changes were detected in 12 tumors (43%) with a mean of 1.4 changes per sample (range: 1 to 7). Out of 12 tumors associated with pregnancy or Gardner's syndrome, only two displayed changes. The minimal common regions of the most frequent gains were 1q21 (39%), chromosome 20 (32%), and 9p12 (21%). No high-level amplifications were detected. Losses of DNA sequences were two times less frequent than gains and the minimal common regions of the most frequent losses were 6q16–q21 (14%), 5q14 (11%), and 13q21–q31 (11%). *Genes Chromosomes Cancer 23:183–186, 1998.*

The term "desmoid tumor" is often used as a synonym for "deep fibromatosis." These are rapidly growing tumors that principally involve deeper structures and behave more aggressively than fascial fibromatoses (Enzinger and Weiss, 1995). Despite the destructive and invasive pattern of growth, which includes infiltration of the surrounding tissue, desmoid tumors are generally considered benign fibrous tissue tumors (Chang et al., 1989). Abdominal desmoid tumors have a tendency to occur in women during or following pregnancy (Enzinger and Weiss, 1995). Approximately 50% of the desmoid tumor cases have clonal chromosomal abnormalities (Dal Cin et al., 1994, 1995; Dangel et al., 1994; Fletcher et al., 1995; Mertens et al., 1995; Bridge et al., 1996; Qi et al., 1996).

Desmoid tumors affect more than 10% of the patients with familial adenomatous polyposis (FAP) of the colon (Clark and Phillips, 1996). Based on the Finnish Polyposis Registry, the cumulative lifetime risk has been estimated to be as high as 21% (Heiskanen and Järvinen, 1996). Desmoid tumors in FAP patients usually occur in the mesentery and/or abdominal wall, commonly following surgical intervention. This condition, often associated with multiple osteomata and keratinous cysts of the skin, is known as Gardner's syndrome. The defective gene, adenomatous polyposis coli (*APC*), has been mapped to 5q15–q22 (Bodmer et al., 1987; Kinzler et al., 1991).

Comparative genomic hybridization (CGH) has been shown to be a powerful tool for screening amplified and deleted DNA sequences (Kallioniemi et al., 1992; Knuutila et al., 1998). In this study, we demonstrated novel recurrent DNA copy number gains at 1q21 in desmoid tumors.

The material consisted of 28 samples from desmoid tumors collected from the pathology laboratories in the Helsinki University Central Hospital and the Department of Pathology, University of Helsinki. Seven of the patients were women whose pregnancy had ended less than a year before the diagnosis of desmoid tumors, and five of the patients had Gardner's syndrome (Table 1). Histopathological and clinical characteristics of the cases are presented in Table 1. DNA from paraffin-embedded tissue sections from all tumors was extracted as described by Miller et al. (1988).

CGH was performed using direct fluorochrome-conjugated DNAs for all samples according to a recently reported protocol (El-Rifai et al., 1997). To confirm the results by a standard labeling system, reverse labeling was performed for tumors 17–28 as described elsewhere (Larramendy et al., 1997b).

Hybridizations were analyzed using an Olympus fluorescence microscope and the ISIS digital image

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TABLE 1. Histopathological and Clinical Characteristics and DNA Copy Number Changes in 28 Desmoid Tumors

Patient number, sex, age	Patient code	Associated with	Tumor location and size[a]	DNA copy number changes
1, F, 38	XP93-3648		Thigh 4.5, P	No change
2, M, 49	XP93-3722		Shoulder 6, R	No change
3, M, 14	L90-558		Thigh NA, R	No change
4, F, 32	XP93-2366		Trunk 6, P	No change
5, F, 45	833-80		Abdominal wall 8, P	No change
6, M, 29	XP95-2832		Shoulder 20, P	No change
7, F, 32	XP91-6509		Thigh 8.5, P	+1q21–q23,+20
8, M, 20	XP91-5156		Mesenterium 40, 9 kg, P	+1q21,−6,+20
9, F, 52	XP94-3355		Shoulder 7, R	+1q21–q23,+20
10, F, 55	XP94-2732		Thoracic wall 5, P	+1q21–q25,−5q21–q22,+9p13–q21,+20
11, M, 70	XP92-0371		Mesenterium NA, P	+1q21–q23,−5q15–q23,+20
12, M, 42	XP94-1006		Thoracic wall NA, R	+1q21–q23,−13q21–q31
13, F, 67	XP95-0647		Trunk 7, P	+1q21–q22,+9p12–q21.2,+20
14, F, 45	XP90-3953		Buttock 10, R	+1q21–q23,−4q,−5q21–q22,−6cen–q24,+7p11.2q11.2,+9p12–p13,+20
15, F, 40	XP94-2374		Upper arm 6, R	+1q21,+9p12–q21.2,−13q21–qter,+20
16, F, 68	XP87-9822		Neck NA, R	+1q21–q23,−6q15–q21,+7cen–q11.2,−9pter–q21,−13q21–q33
17, F, 29	XP96-1006	Pregnancy	Rectus 6, P	No change
18, F, 32	XP94-3342	Pregnancy	Rectus 4, P	No change
19, F, 30	XP96-2457	Pregnancy	Rectus 3.5, R	No change
20, F, 29	XP94-13245	Pregnancy	Rectus NA, P	No change
21, F, 33	K93-5587	Pregnancy	Rectus 4.5, P	No change
22, F, 29	K91-10966	Pregnancy	Abdominal wall 4, P	No change
23, F, 36	XP95-2257	Pregnancy	Rectus 6, P	−6cen–q24, +9p12–p13, +20
24, F, 37	XP95-12026	Gardner's syndrome	Mesenterium 4, R	No change
25, M, 30	XP95-2796	Gardner's syndrome	Mesenterium 40, 14 kg, P	No change
26, F, 28	XP94-3791	Gardner's syndrome	Mesenterium NA, 1.9 kg, P	No change
27, M, 25	XP96-14079	Gardner's syndrome	Thoracic wall NA, 9 kg, R	No change
28, 17, M	XP92-3064	Gardner's syndrome	Groin 7.5, P	+1q21, +9p12

[a]Greatest dimension in centimeters, weight; NA, data not available; P, primary tumor; R, recurrent tumor.

analysis system (MetaSystems Hard & Software, Altlussheim, Germany). Chromosomal regions were interpreted as overrepresented when the green-to-red ratio was higher than 1.17 (gains) or 1.5 (high-level amplifications), and as underrepresented when the ratio was lower than 0.85 (losses) (El-Rifai et al., 1997).

Of the 28 tumors, 12 (43%) had changes with a mean value of 1.4 aberrations per sample (range: 1 to 7) (Table 1). DNA copy number changes were observed in only one of the seven tumors associated with pregnancy (patient 23) and in one of the five tumors from Gardner's syndrome patients (patient 28).

The minimal common regions of the most frequent gains were narrowed down to 1q21 (11 patients, 39%) and the whole chromosome 20 was gained in nine patients (32%; see Fig. 1). Gain at 1q21 was not observed in tumors associated with pregnancy or with Gardner's syndrome (except one, patient 28). Gain in 9p was narrowed down to 9p12 in seven patients (21%) and gain at 7cen–q11.2 was observed in 2 patients (7%). No high-level amplifications were detected.

The minimal common regions of the most common losses were 6q16–q21 (14%), 5q14–q15 (11%), and 13q21–q31 (11%) (Table 1, Fig. 1). Other losses were observed once in 4q and 9pter–q21 (4%) (Table 1).

Our novel finding is a recurrent gain at 1q21. This gain was observed only once in a desmoid tumor from our Gardner's syndrome patient (no. 28), but never in the tumors associated with pregnancy. Thus, the developmental pathway in regular desmoid tumors may differ from that in desmoid tumors associated with pregnancy or Gardner's syndrome.

The 1q21 gain has been detected frequently in several other tumors (Knuutila et al., 1998), especially in sarcomas (Tarkkanen et al., 1995; Forus et al., 1996; Szymanska et al., 1996; Armengol et al., 1997; Larramendy et al., 1997a). Forus et al. (1996)

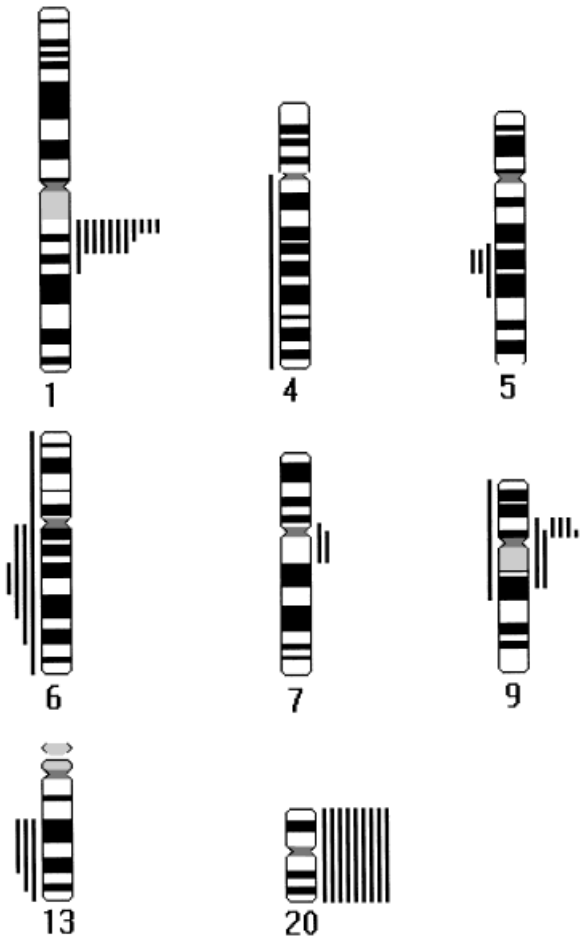

Figure 1. Summary of DNA copy number changes in 28 desmoid tumors. Losses are shown on the left and gains on the right of each chromosome. Each line represents a change seen in one sample.

have recently reported that the *FLG*, *NTRK1*, and *SPRR3* genes, mapped to 1q21, are frequently amplified at 1q21–q22 in sarcomas. Moreover, because all sarcomas with amplified 1q21–q22 by CGH did not show all these loci to be amplified by molecular studies, the region has been suggested to harbor an unknown target gene for the 1q21–q22 amplicon in human sarcomas (Forus et al., 1996).

In addition to 1q gains, overrepresentations affecting the whole chromosome 20 were observed in 32% of the tumors. The nonrandom occurrence of trisomy 20 has been observed previously in desmoid tumors and it has been suggested that +20 and/or +8 might contribute to aberrant cell proliferation in a wide spectrum of pathological fibrous proliferations (Fletcher et al., 1995). In infantile fibrosarcoma, the association of these two trisomies has so far only been reported to appear simultaneously (Mitelman, 1994).

In our material, CGH was unable to detect any gain on chromosome 8. The frequency of trisomy 8 in desmoid tumors evaluated by standard karyotype analysis is about 8% (7 out of 84 patients reported so far) (Karlsson et al., 1988; Bridge et al., 1992, 1996; Dal Cin et al., 1994, 1995; Dangel et al., 1994; Fletcher et al., 1995; Mertens et al., 1995; Qi et al., 1996). Based on the small number of cases studied, the discrepancy between our CGH findings and those by karyotype analysis may be fortuitous. Alternatively, the discrepancy may be explained by the insensitivity of CGH to reveal changes that are present in less than 50% of the cells.

Gain at 9p12 was seen in three cases (11%). This gain is not known to be recurrent in any other tumors. Loss at 5q14–q15 was observed in three tumors (11%). Previous standard karyotype analyses have revealed del(5q) to be a recurrent aberration in desmoid tumors, including tumors from Gardner's syndrome patients (Bridge et al., 1992, 1996; Dangel et al., 1994). The adenomatous polyposis coli (*APC*) gene, mapped to 5q15–q22, encodes a large (312 kD) protein involved in the intracellular transmission of cell-adhesion signals (Polakis, 1995) and in blocking cell cycle progression from G0/G1 to S-phase (Baeg et al., 1995). Recently, the presence of a "desmoid" modifier gene closely linked in cis to codon 1924 of the *APC* gene has been demonstrated to cause somatic loss of the wild-type allele and to lead to tumor development (Eccles et al., 1996).

Losses at 13q21–q31 were observed in 11% of the tumors. This loss has been observed in several other sarcomas and other tumors (Larramendy et al., 1997a; Knuutila et al., 1998). However, the loss observed in the present study does not seem to involve 13q14, where the *RB1* gene is located. Thus, a suppressor gene other than *RB1* may be involved in desmoid tumors.

A better understanding of the pathogenetic pathways in the initiation and progression of desmoid tumors, especially those associated with pregnancy and Gardner's syndrome, requires molecular studies of 1q, 9p, and 20 gains, as well as of 6q and 13q losses—genetic changes that were found frequently in this study.

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