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Identification of a Recurring Translocation Site Involving Chromosome 6 in Human Malignant Melanoma[1]

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ABSTRACT

The recognition of recurring sites of chromosome change in human cancers has pinpointed the location in the genome of several important growth-regulatory sequences (*e.g.*, cellular oncogenes). This report details the finding of a recurring translocation site involving the long arm of chromosome 6 (6q) in malignant melanoma. We have observed a translocation (t) between chromosomes 1 and 6 in five different cases of malignant metastatic melanoma. All five melanomas evidencing t(1;6) involved band regions 6q11-13, while two different regions of chromosome 1 (p22, q12-q21) were shown to be translocated to 6q. In reviewing previously published cases of melanoma, an additional two cases of t(1;6) and 13 cases of other translocations to 6q11-13 have been identified. Chromosome 6q contains several biologically important gene sequences including the proto-oncogenes *ros, myb,* and *mas1*. However, based on current mapping studies, the breakpoint of this translocation (6q11-13) is not within the region encoding these sequences. By analogy to other systems, molecular analysis of the translocation breakpoints may identify a gene(s) which plays a role in melanoma tumorigenesis.

INTRODUCTION

Specific chromosomal translocations have characterized numerous types of human cancers but particularly those of hematopoietic lineage (1–4). Recurring chromosomal alterations in Burkitt's lymphoma and chronic myelogenous leukemia have been clearly implicated in the altered expression of proto-oncogenes (*i.e.*, c-*myc*, c-*abl*), a finding which strongly supports the notion that chromosomal changes are important in carcinogenesis (1).

Recurring translocations of the specificity and frequency characterizing hematopoietic cancers (*e.g.*, the Philadelphia chromosome in chronic myelogenous leukemia) have not been recognized in the majority of solid tumors, including malignant melanoma. However, several chromosomes appear nonrandomly involved in melanoma, most notably chromosomes 1, 6, 7, 10 (5–10), and 19 (11) (for review see Ref. 12). The observation of chromosome 6 alterations, particularly deletions involving the long arm, are perhaps the most frequent alteration recognized in this neoplasm (4–7). We now report the finding in five cases of malignant melanoma of translocations involving chromosomes 1 and 6. The breakpoints of all five cases involved band region 6q11-13, although two different regions of chromosome 1 (p22, q12-q21) were shown to be translocated to 6q. Coupled with the recognition in the literature of numerous additional examples of translocations involving 6q11-13, these data support the notion that a gene(s) at 6q11-13 may be involved in the etiology or progression of melanoma.

MATERIALS AND METHODS

The basis for these observations originates from our recent examination of 29 cases of direct preparations of metastatic malignant melanoma (13). Data from melanoma tumors were obtained within 1 week of culture initiation. In cases CC-9 and T84-097, cells were grown in agar culture (14), while cases T87-093 and T87-096 were grown in short-term liquid culture (15). Methods for chromosome banding (G- and C-) have been described in detail elsewhere (15). No karyotypically normal cells were observed in any tumor culture. C-banding (to recognize constitutive heterochromatin) was performed on all cases with t(1;6) in order to assist the breakpoint location relative to 1q11-12. Examination of a minimum of 15 cells and four banded karyotypes was performed on all cases. The description of chromosome alterations conforms to International System for Human Cytogenetic Nomenclature (16).

RESULTS

During the cytogenetic investigation of 29 cases of malignant melanoma, five cases were observed to contain the t(1;6) chromosome. The modal chromosome number of these five tumors varied from 61 to 92. Table 1 provides complete karyotypic information on these five cases, with Tables 2 and 3 providing a summary of the abnormalities of chromosomes 1 and 6 from these five cases, as well as the combined data from other laboratories reporting 6q translocations.

As summarized in Tables 1–3 and illustrated in Fig. 1, four cases exhibited clonal nonreciprocal translocations between 1q12-21 and 6q11-13 [t(1;6) (q12-21;q11-q13)]. In one case the proximal short arm (p22) was translocated to 6q11-13. In reviewing the published literature, an additional two cases of t(1;6) (q11-q12;q11-q13) were identified (Table 1), further strengthening the nonrandom nature of this translocation.

In addition to the frequent finding of t(1;6), translocations between 6q11-13 and other chromosomes were also observed. Three cases of t(5;6) and two cases of t(3;6) were observed, as well as single cases of t(4;6) and t(6;17). Also, several cases with unidentifiable chromosomal segments translocated to 6q11-13 t(6;?) (q11-13;?) have been reported (Tables 2 and 3). Fig. 2 provides a pictorial summary of the proposed breakpoints and derivative chromosomes resulting from translocations to 6q11-13.

Translocations involving 6q11-13 were shown to be present in both the direct cultures of malignant melanomas (Table 2) as well as being retained in established melanoma cell lines (Table 3). In one case (CC-9) it was possible to examine both direct tumor material and two subsequently established cell lines from the same tumor for the presence of the t(1;6) (16). The t(1;6) was retained in both direct and cultured tumor cells suggesting this abnormality is not an artifact of *in vitro* culture.

DISCUSSION

The chromosomal profile of malignant melanoma has been most frequently characterized as containing structural alterations of chromosomes 1, 6, 7, 10, and 19 (4–13). Recently, a specific translocation defining a subset of melanomas was described: t(1;19) (q12;p13) (11). This abnormality was observed in cells from three patients, with the suggestion made that band region 19p13 might be the site of a gene important in melanoma carcinogenesis (11). The breakpoint on chromosome 1 in the t(1;19) (q12;p13) appears to involve the same band region on

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Table 1 *Chromosome alterations from five cases of malignant melanoma*

Case no.	Karyotype
CC-9	71,XX,+del(1)(q42),+3,+3,+5,+t(1;6)(q21;q13)[4 copies], +7,+7,+7,+8,+9,+12,+13,+13,+15,+16,+17,+17,+18,+19, +20,+20,−21,+2 Umar's,+DMs
T84-097	65-70,XX,+del(1)(q42),+t(1;6)(q11;q13),+del(6)(q15), +t(11;?)(p15;?)*
T87-069	61,XX,+1,−2,+t(2;?)(q31;?),+3,+5,−6,+t(1;6)(q11;q11), +7,+8,+9,+del(11)(p15),+12,+17,+20,−22,+5 Umar's
T87-093	92,XYY,−3,+t(3;?)(p25;?)[2 copies],+der i(3q), +4,+4,+5,+5,+del(6)(q15),+t(1;6)(q11;q11) [2 copies],+7,+7,+7,+11,+11,+11,+t(12;?) (q21;?),+t(13;21)(p11;q11)[2 copies], +t(13;?)(q34;?),+13,+13,+16,+16,+17,+17, +18,+18,+19,+19,+19,+19,+2,+20,+20,+20,+21, +21,+22,+9 Umar's
T87-096	75,XX,+1,+t(1;?)(p22;?),+2,+3,+3,+4,+5,+6,+t(1;6) (p22;q11-13),+8,+11,+12,+14,+20,+20,+21,+22,+7 Umar's

* Clonal numeric changes were not described because of karyotypic heterogeneity and a lack of a distinct modal chromosome number.

chromosome 1 as five of the cases of t(1;6) in this study. Band region 1q11-12 represents a major site of constitutive heterochromatin and therefore is a region of the genome with a relative paucity of gene activity. For this reason, the contribution of sequences within 1q11-12 to either the t(1;6) or t(1;19) is currently unclear. Chromosome abnormalities other than those involving 1 or 6 are also frequently observed in malignant melanoma, including: translocations involving chromosome 7q11 (5, 9, 11) and deletions involving chromosome 10q24-26 (18).

Alterations of chromosome 6 in melanoma have included the frequent finding of isochromosomes of the short arm [iso(6p) (10)] and particularly deletions of the long arm [del(6q) (4–7, 12)]. However, of interest to this report, the region most frequently deleted on 6q(q21-23) results in loss of band regions distal to those involved in the t(1;6) translocations (Fig. 2) (12, 13). Our results suggest that the translocation site involving 6q11-13 defines a region of chromosome 6q which is significantly removed (particularly at the nucleotide level) from those band regions frequently lost via chromosomal deletion in malignant melanoma. However, even though the cytological location of the translocation site is distant to the most common area lost in 6q deletions (Fig. 2), it is possible that the translocation and the aforementioned deletion of 6q may be related. Specifically, recent examination of human colonical neoplasms have suggested that chromosomes 5 or 17 may be involved in nonreciprocal translocations near their centromeres, leading to loss of genomic sequences distal to the translocation breakpoint (19). Therefore, by analogy to colon carcinoma, the possibility exists that the nonreciprocal translocations described in this report could represent a means of removing sequences on distal 6q, providing an alternative mechanism for the loss of heterozygosity of 6q alleles in melanoma. This possibility is currently being investigated via restriction fragment length polymorphism analysis.

Recently, several biologically important gene sequences, including proto-oncogenes, have been assigned to 6q (for review see Reference 20). These include *ros* [6q16→q22] (21), *mas1* (21–22), and *myb* [6q24] (23–25). Of further interest, *myb* expression has been shown to be disregulated in leukemias containing structural chromosome alterations (including interstitial deletions) of 6q (26). However, to date we have failed to observe any structural alterations of c-*myb* in any of 20 melanomas tested (using standard electrophoresis and Southern blotting), a finding supported by other investigators (27).

Table 2 *Chromosomal data from melanomas with 6q translocations*

Identification no.	No. cells analyzed	Modal chromosome no.	Abnormalities of chromosomes 1 or 6	Ref.
T87-093	25	92	t(1;6)(q11;q11) del(6)(q15)	This report
T87-096	25	75	t(1;6)(p22;q11–13) t(1;?)(p22;?)	This report
T84-097	50	65-70	t(1;6)(q11;q13) del(1)(q11) del(6)(q15)	This report
CC-9[a]	81	70	t(1;6)(q21;q13) del(1)(q42)	This report
MM214	20	89	t(1;6)(q11;q11)	29
NG	50	50	t(3;6)(p21;q14.1) der(6) t(3;6)(p22.1;p21.3) t(6;11)(p21.1;q12)	10
Case 3	39	61-68	t(3;6)(q29;q13) t(1;13)(q21;q34) del(6)(q21q13)	5
Case 4	38	65-68	t(5;6)(q35;q13) i(1q) del(6)(q13) del(6)(q13q23)	5
MM253-1	20	66	t(5;6)(q11;q11) t(1;?)(p13;?)	29
RW	NG[b]	NG	t(5;6)(q13;q13)[c]	6
Case 1	T 33	47	t(6;7)(q11;qter) t(1;8)(p13;p12) del(1)(p22) t(1;2)(p23;p22) t(6;?)(q23;?)	5
WP-2	T 25	66	t(6;17)(p11;q11) t(1;12)(p34;q15) t(1;12)(p21;q21) t(1;15)(q32;q25) t(1;6)(q11;q24)[d]	9

[a] Two cell lines from the CC-9 tumor were established, both of which maintained the t(1;6).
[b] NG, not given in text.
[c] Reinterpretation of author's previous results.
[d] The breakpoint along 6q in this case (6q24) is significantly distal to 6q11-13.

Table 3 *Chromosomal data from melanoma tumor cell lines with 6q translocations*

Identification no.	No. cells analyzed	Modal chromosome no.	Abnormalities of chromosomes 1 or 6	Ref.
T87-069	17	61	t(1;6)(q12;q11)	This report
HA-A, HA-L[a]	81	70	t(1;6)(q21;q13) del(1)(q42)	17
TCH3119	≥20	NG[b]	t(1;6)(q12;q13)[c]	7
COLO297	50	87	t(4;6)(q12;q11) del(1)(p13) t(1;2)(p34;p23) t(1;3)(q11;p13)	30
COLO349	50	80	t(6;?)(q11;?) t(1;?)(p12;?)	30
TCH3114	≥20	NG	t(6;?)(q13;?)[c]	7
TCH3115	≥20	NG	t(6;?)(q14;?)[c]	7
TCH3116	≥20	NG	t(6;?)(q14;?)[c]	7
TCH3636	≥20	NG	t(6;?)(q14;?)[c]	7

[a] Two cell lines from the CC-9 tumor were established, both of which maintained the t(1;6).
[b] NG, not given in text.
[c] Breakpoints kindly provided by authors (not given in Reference).

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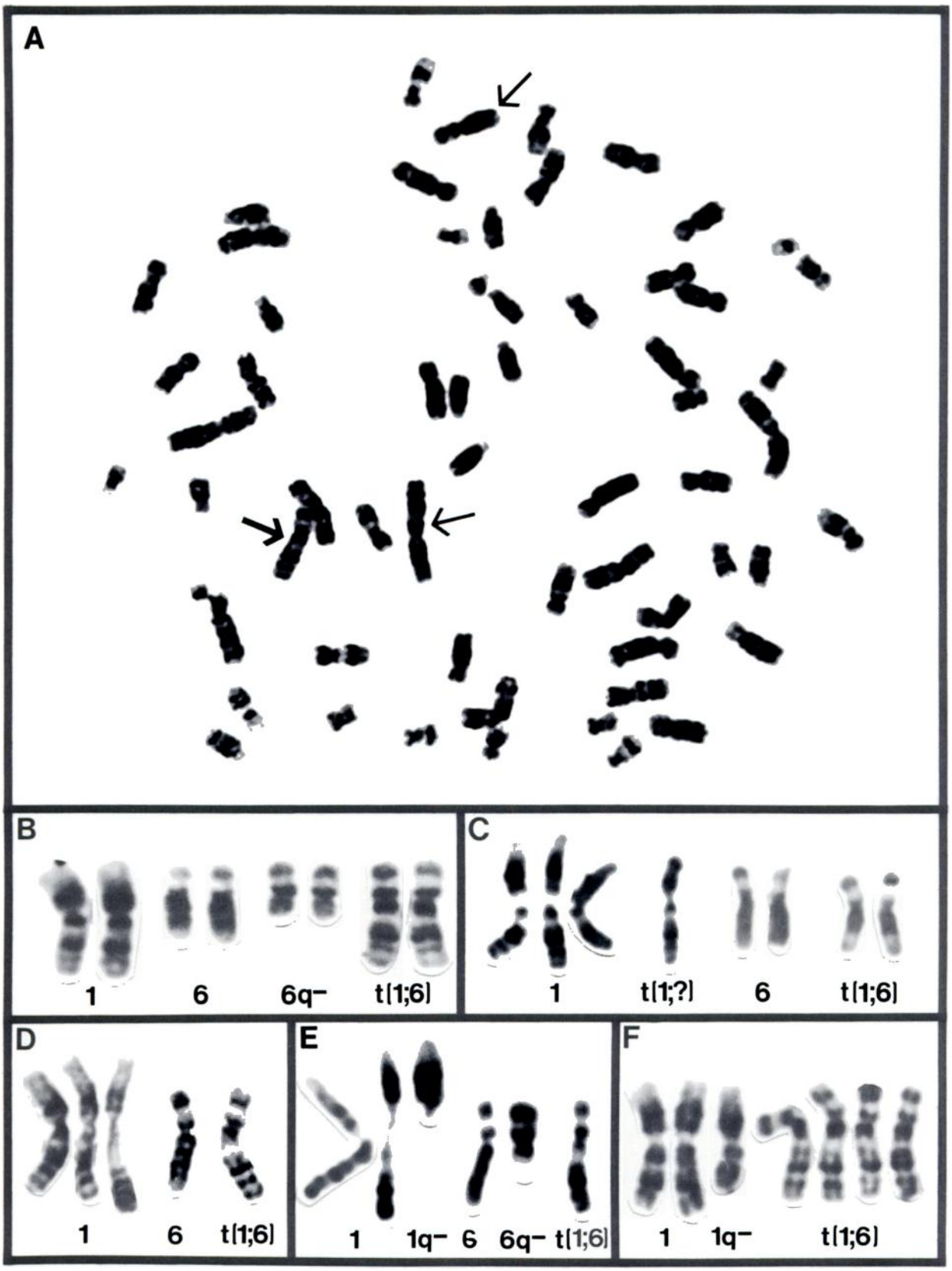

Fig. 1. Representative examples of G-banded cells from five cases of melanoma displaying a translocation between chromosomes 1 and 6. Detailed description of chromosome breakpoints are provided in Table 1. *A*, G-banded metaphase of case T87-069. *Thin arrows*, normal chromosome 1 and 6 for comparison with the t(1;6) (*bold arrow*). Normal and clonal structural abnormalities of chromosomes 1 and 6 in cases T87-093 (*B*), T87-096 (*C*), T87-069 (*D*), T84-097 (*E*), and CC-9 (*F*).

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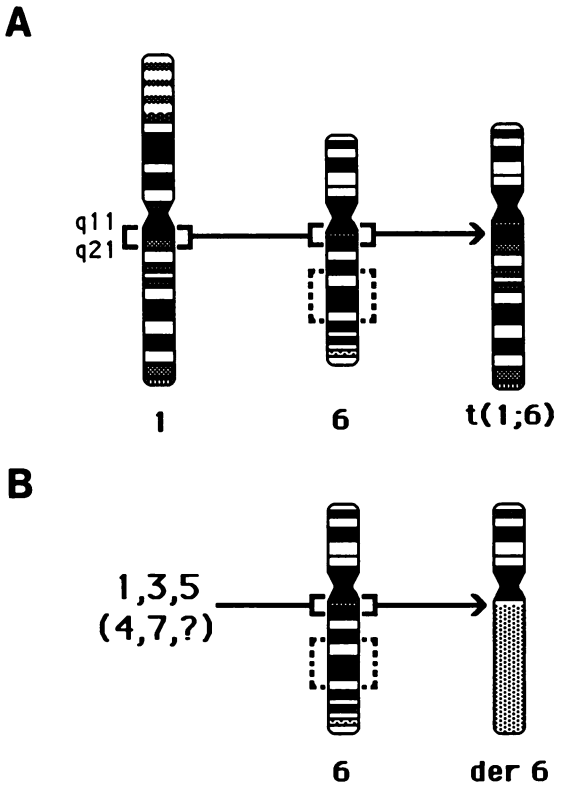

Fig. 2. Idiogram diagramming breakpoints and derivative chromosomes resulting from translocations of various chromosomes to 6q11-21. *A*, breakpoints involving chromosomes 1 and 6 with resulting derivative t(1;6). *Arrows to chromosome 1*, band region involved in translocation with 6q11-13 (*solid brackets*). *B*, chromosomes 1p, 3, 4, 5, 7, and unidentified chromosomal segments (?) were also shown to translocate to 6q11-13 (see Table 1). *Dotted brackets*, region of 6q most frequently involved in simple deletions (see text).

Finally, although their significance in relation to malignancy is unclear, fragile sites have been shown to map to tumor-associated chromosomal breakpoints (28). A common fragile site (FRA6D) has been mapped to 6q13 (28), although its role, if any, in the oncogenic process is currently indeterminate.

In summary, the translocation site described in this report characterizes seven cases of t(1;6) and an additional 13 cases in which other chromosomal regions have been translocated to 6q11-13. This nonrandom involvement of band region 6q11-13 in these 20 unrelated patients with malignant melanoma strongly suggests that this translocation site represents a tumor-related chromosome change characterizing a subset of patients with this disorder. By analogy to other systems, it is possible that molecular analysis (which is currently underway) of this recurring translocation site may identify sequences important in melanoma carcinogenesis.

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