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CHROMOSOME ALTERATIONS IN HUMAN MALIGNANT MELANOMA

Jeffrey M. Trent*
Stanley P.L. Leong•
Frank L. Meyskens≠

University of Arizona
Arizona Cancer Center
Departments of Radiation Oncology,*
Internal Medicine≠
and
Surgery•
Tuscon, Arizona 85724

Over the past five years, there has been a tremendous advance in our understanding of molecular genetic changes underlying oncogenesis. During this time, the uniting of cytogenetics with molecular biology has provided a powerful experimental approach to address mechanisms of cancer causation. The fundamental conclusion which may be drawn from the cytogenetic study of many tumors type is that recurring sites of chromosome change pinpoint the location of growth regulatory sequences (e.g., cellular oncogenes). Moreover, it is now clear that the recognition of specific chromosome abnormalities can also have important diagnostic and prognostic implications. This brief review will first summarize the recurring sites of chromosome alterations observed in human malignant melanoma and then discuss the relationship of human cellular oncogenes to these alterations. The central theme which underlies this review is that chromosome alterations represent the byproduct of molecular events which will prove to play a causative role in melanoma carcinogenesis.

RECURRING SITES OF CHROMOSOME CHANGE IN MALIGNANT MELANOMA

Overview

There is now strong evidence that the overwhelming majority of malignancies (including malignant melanoma) display recurring sites of chromosome change (7,25). Further, as mentioned previously, the nonrandom nature of these chromosomal abnormalities has been extremely useful biologically (in localizing the sites of oncogenes) as well as clinically (as diagnostic and prognostic markers) (7,9,19,24,25). However, to date, it is the hematopoietic malignancies which have most readily (and successfully) yielded to molecular/cytogenetic analysis. For example, chromosome breakpoint analysis of specific translocations characterizing chronic myelogenous leukemia (CML) and Burkitt's lymphoma (BL) have directly implicated chromosomal alterations in the altered expression (c-*myc*, BL) or altered produced (*c-abl*, CML) of cellular oncogenes (9,19).

The identification in human solid tumors of specific chromosomal alterations has lagged behind the study of the leukemias and lymphomas. However, over the past decade, significant advances have occurred in methodology for both culture and chromosome harvesting of human solid tumors (28). Accordingly, an ever-increasing number of solid tumors have been shown to demonstrate tumor associated chromosome alterations (for review see 25). The following sections will provide background information on the frequency and specificity of chromosomal alterations in malignant melanoma. A brief discussion of the general patterns of chromosome rearrangements in melanoma will first be presented, followed by discussion of those chromosomes nonrandomly altered in this disorder.

General Patterns of Chromosomal Rearrangements

Several studies have appeared characterizing chromosomal alterations in malignant melanoma (3,4,6,8,12,15-18,20,22,27). However, two problems arise when considering a comprehensive review of the literature in this disorder. First, the majority of cytogenetic studies to date have utilized established melanoma cell lines. Second, virtually all cytogenetic analyses of melanomas have been performed on metastatic rather than primary tumors. For these reasons, the chromosome alterations described in this chapter will by necessity focus on metastatic melanoma. In the furture, significant effort will need to be focused on chromosomal changes characterizing primary tumors (as well as premalignant lesions -- e.g. dysplastic nevi).

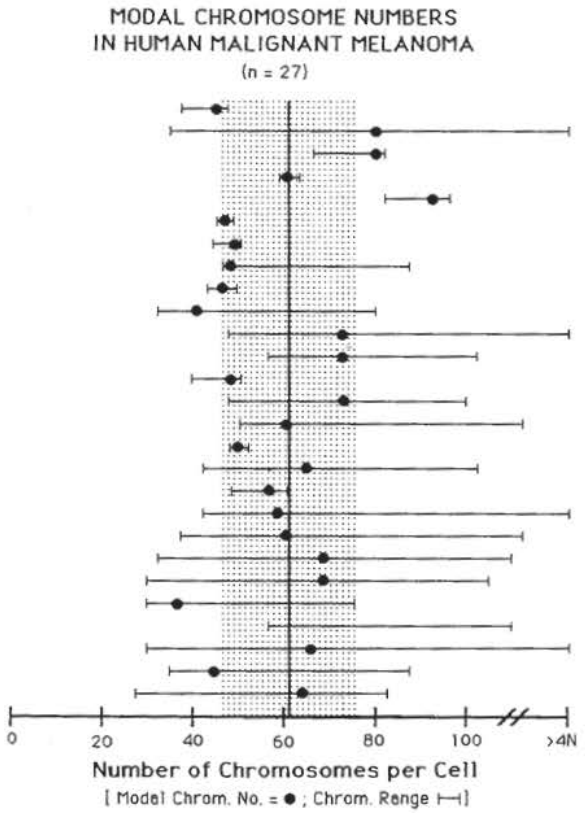

Figure 1: Graph illustrating the modal chromosome number and range of chromosome per cell observed from 27 cases of human malignant melanoma. The closed circle (●) represents the chromosome number per cell most frequently observed (the modal number) within a given patient. The bars (—) reflect the range of chromosomes per cell observed for each patient. The overall mean chromosome number for the entire patient population was 60.9 chromosomes/cell, with the cross-hatching reflecting the standard error around the mean (+/- 14.2).

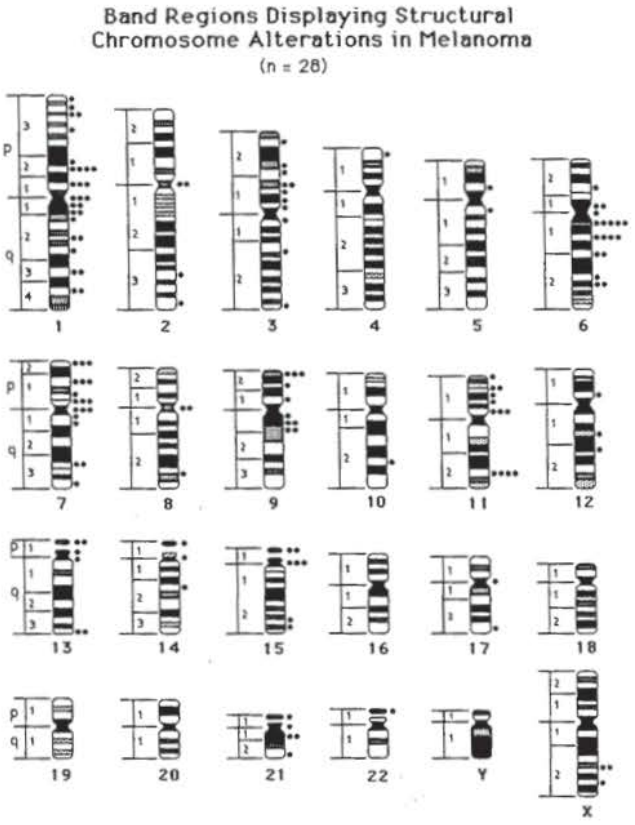

Figure 2: Idiogram of G-banded human chromosomes documenting the band regions displaying structural chromosome alterations. The solid circles ( ) illustrate the sites and frequency at which chromosomal band regions were involved in structural alterations from 28 cases of malignant melanoma (see text).

Table 1. List of Chromosome Aberrations in Malignant Melanoma*

Region or band	Type of Aberration	Status+	References
1p22-p11	Deletions, translocations	I	Kakati et al. (1977) Becher el al. (1983) Balaban et al. (1984) Pedersen et al. (1986) Parmiter et al. (1986)
1q11-q12	Translocations, duplications	I	Atkin & Baker (1981) Becher et al. (1983) Ochi et al. (1984) Pedersen et al. (1986) Parmiter et al. (1986)
6p11-q11	i(6p), translocations	II	Kakati et al. (1977) Becher et al. (1983) Balaban et al. (1984) Rey et al. (1985)
6q11-q27	Deletions, translocations	I	Trent et al. (1983) Becher et al. (1983) Pathak et al. (1983) Balaban et al. (1984) Cowan et al. (1986) Parmiter et al. (1986) Pedersen et al. (1986)
7q11	Translocation	II	Kakati et al. (1977) Becher et al. (1983) Parmiter et al. (1986) Pedersen et al. (1986)

*From Bloomfield C, Trent J. and Van Den Berghe H. Report on the Committee on Structural Chromosome Changes in Neoplasia (HGM9). Cytogenetic and Cell Genetics, in press (1988).
+The criteria for each status as per HGM9 recommendations were: Status I - at least two laboratories have reported the abnormality in a total of five cases; Status II - at least three cases have been reported from two different laboratories or at least five cases from one laboratory.

Despite the aforementioned difficulties of harvesting chromosomes from solid tumors and the possible biasing of the patient population by focusing on metastatic disease, significant evidence has accumulated suggesting a nonrandom pattern of chromosome change in malignant melanoma. Figure 1 provides a summary of the modal chromosome numbers (and range around the mode) from 27 consecutive cases of malignant melanoma studied in the author's laboratory. As can be observed, significant variation in modal chromosome number occurred, as well as significant variability in the range of chromosomes per cell observed within each case. In general, the modal chromosome number of most melanomas appears hypotriploid (x=60.9 chromosomes/cell) with modal chromosome numbers ranging from <40 - >90 chromosomes/cell.

Despite the often significant range of chromosome numbers/cell within a given tumor, recurring (i.e. clonal) chromosomal alterations are recognizable in virtually every case of metastatic melanoma, and the recurring nature of these alterations becomes increasingly apparent when sufficient cases are studied. For example, Figure 2 provides a pictorial summary of all chromosomal band regions involved in structural chromosome rearrangements from 28 cases of malignant melanoma studied in our laboratory. As can be observed, the pattern of chromosome change is clearly nonrandom. In this series of patients, chromosome 1 was involved in almost 20% of the chromosome alterations recognized, whereas chromosomes #16, #18, #19, #20, #22 and Y were never observed to participate in structural chromosome rearrangements. Furthermore, this variation is not merely a reflection of the relative size (and accordingly DNA content) of individual chromosomes, as the frequency of chromosomal alterations involving similarly sized chromosomes can vary significantly (e.g. #2 vs. #3; #7 vs. #8; #11 vs. #12 -- Figure 2). The results from our laboratory correlate well with previously published findings in malignant melanomas (3,4,6,8,12,15-18,20,22,27). In summary, chromosomes #1, #3, #6, #7, and #11 are the most frequently involved in structural abnormalities in this disorder.

Table 1 provides a listing of the currently recognized recurring chromosomal alterations in malignant melanoma. This list is based on the most recent review of the world literature performed by the Committee on Structural Chromosome Changes in Neoplasia of the Human Gene Mapping (HGM) Workshop (7) . By HGM criteria, deletions, translocations, or isochromosome formation of chromosomes #1, #6, and #7 have been reported in sufficient frequency to be considered nonrandom alterations in melanoma [Table 1].

Figure 3 provides a representative G-banded karyotype from cells directly harvested from a malignant melanoma. This

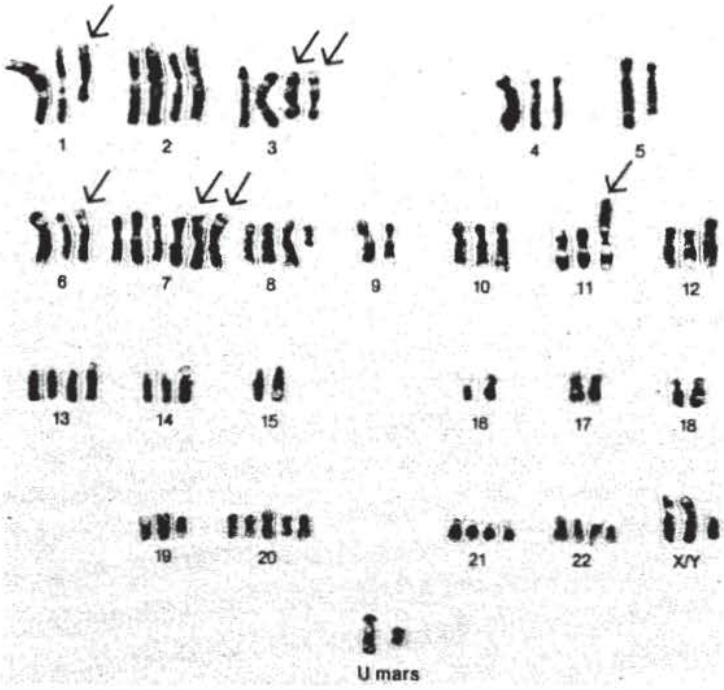

Figure 3: Representative G-banded karyotype from a malignant melanoma. The arrows document structural or numeric chromosome alterations involving chromosome #1, #3, #6, #7, and #11. Additionally, unidentifiable marker chromosomes (Umars) were also observed in this patient's tumor.

particular cancer evidenced structural and/or numeric alterations of several chromosomes including: #1, #3, #6, #7 and #11. Additionally, it is not uncommon to observe a chromosome which is a byproduct of extensive chromosomal rearrangement and which has a banding pattern so altered as to render its derivation unidentifible. The presence of 1-15 of these "unidentified markers" (Umars) is a common feature of many solid tumors and is found in ~85% of metastatic melanomas examined in our laboratory.

In contrast to the specificity of translocations characterizing many of the human hematopoietic malignancies (i.e. the PH[1] chromosome in CML), it is more common in the solid tumors (including malignant melanoma) for several different chromosome alterations to characterize a given chromosome band region. For example, one often finds several different nonreciprocal translocations as well as deletions of varying size involving the same band region of chromosome 6q (Table 1, Figure 4). Accordingly, although there are exceptions, cytogenetic analysis in malignant melanoma has been most useful in pinpointing "regions" of specific chromosome alteration, rather than identifying a single specific chromosome alteration which is found in the majority of patients. Figure 4 presents pictorial documentation of band regions along chromosomes #1, #6, #7, #11, and #19 which are most frequently involved in chromosome alterations in malignant melanoma.

Chromosomal Segment Representation Profiles

The number and complexity of chromosomal abnormalities occurring within most solid tumors (including malignant melanoma) undoubltedly induce multiple changes in the biology of a tumor cell. For example, translocations move DNA sequences to new sites (and under different regulatory control), often resulting in an altering of gene expression. Similarly, deletions (and unbalanced translocations) can result in loss of gene sequences (related to diploid cells), and nondisjunctional events can produce either additions (e.g. trisomies) or loss (e.g. monosomies), resulting in imbalances of entire chromosomes. In considering the range of abnormalities observed in solid tumors, it is apparent that a major effect of both numeric and structural karyotypic abnormalities is to alter the number of copies of a given chromosomal segment. Accordingly, if preferential patterns of over or under-representation of a chromosomal segment are present, they can be detected and may be of biologic relevance.

We have developed a method to describe the imbalances which result from both numeric and structural anomalies, which we refer to as a "chromosomal segment representation profile" (26). In essence, this approach allows visualization of the gain or

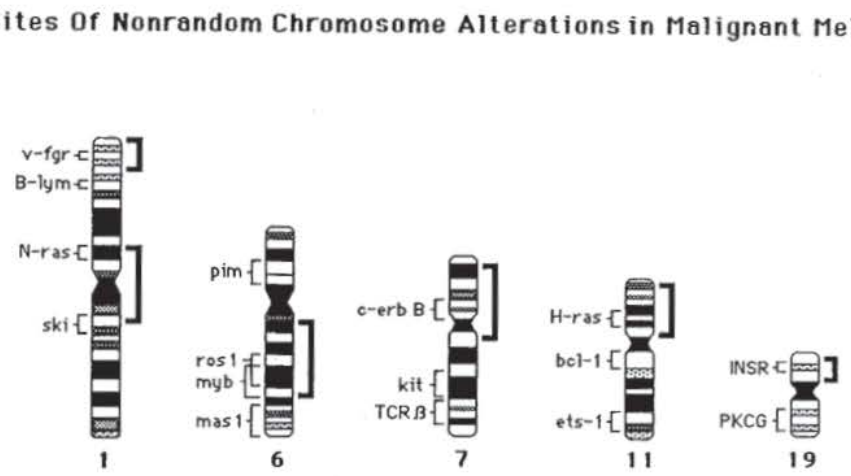

Figure 4: Idiogram of chromosomes #1, #6, #7, #11, and #19 indicating the region of these chromosomes most frequently altered in malignant melanoma. Regional localization of selected cellular oncogenes mapping to these chromosomes are also depicted.

loss of specific chromosome segments, viewed against the background of numerous additional chromosome changes within a tumor. The analysis of chromosome segments is possible only in cases where there is a distinct modal chromosome number (or tight modal range), and where a detailed description of clonal structural chromosome changes is possible. Finally, the profile is expressed in terms relative to normal diploid cells. Very simply, a line is drawn on the right side of a chromosome's caricature (idiogram) when there is a net segment gain, and on the left side when there is a net segment loss. For example, an extra copy (trisomy) of chromosome 7 would be represented by a line on the right side of an idiogram of #7 extending from the tip of the short arm to the terminus of the long arm. Likewise, a partially deleted chromosome 7 which replaces a normal homolog would produce a net loss, and the segment which is lost would be indicated as a line on the left side of the idiogram. Although at first this method for accounting for variations in chromosome segments appears unwieldy, it is in fact very helpful in visualizing chromosomal regions selectively lost or gained against a background of complex chromosome change.

Figure 5 illustrates the results of a chromosome segment representation profile for the four chromosomes most frequently involved in structural chromosomal abnormalities in malignant melanoma: #1, #6, #7, and #11. These results were derived from the complete cytogenetic study of 22 melanoma patients. The modal number for most of these samples was in the hypotriploid range and the most obvious general trend was for the gain of chromosomal segments. However, in comparison to all other chromosomes, the most highly over-represented chromosome was #7. This increase in the number of copies of chromosome 7 was also unique in that it resulted almost invariably from the simple addition of apparently normal homologs. Another striking feature of the chromosome 7 profile is the complete lack of net loss for any portion of this chromosome. In contrast, the loss of segments on distal 6q is readily apparent by this analysis, with gain of the short arm of chromosome 6 resulting from the presence in several samples of isochromosomes of the short arm. The gain of the long arm of chromosome 1 results in part from a specific translocation between chromosomes 1 and 6 (described later in the text). Finally, profiles from chromosome 11 were interesting for two major reasons. First, the instances of net gain and net loss were nearly equal for this chromosome, a situation which was not observed for any other chromosome. Second, the terminal bands on the short arm were excluded from any instance of net gain (although they were included in all instances of net loss).

In summary, segment representation profile analysis allows the study of the gain or loss of specific chromosome segments against a background of complex chromosome change.

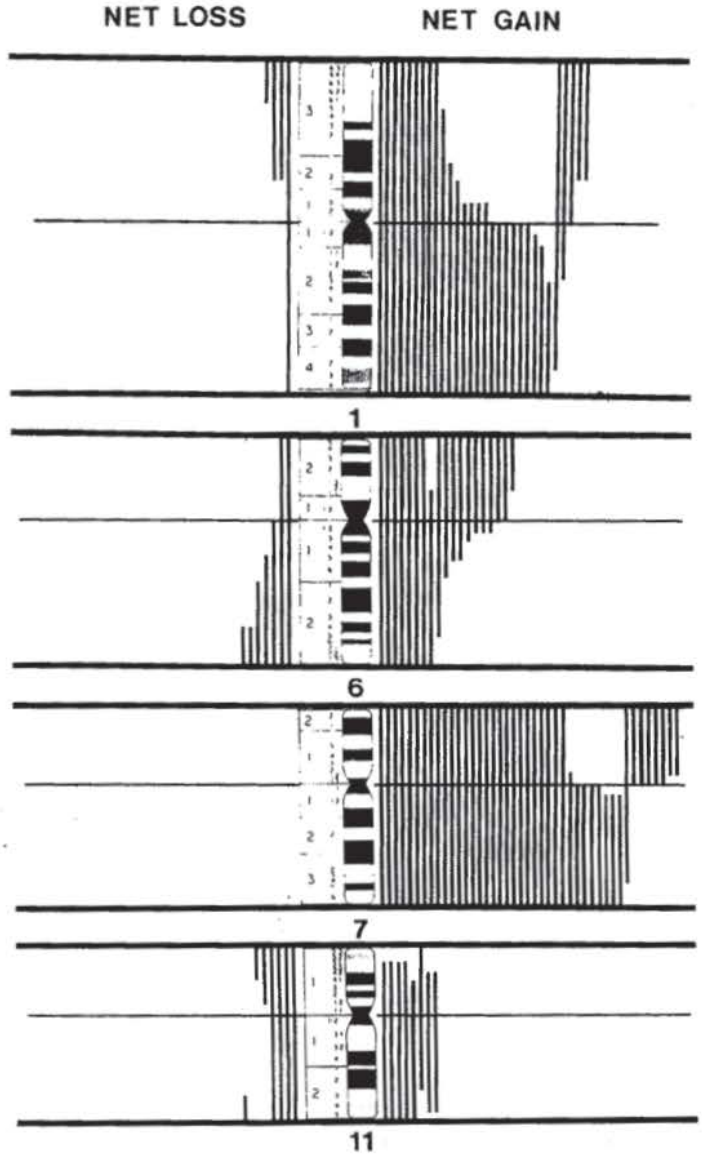

Figure 5: Chromosomal segment representation profiles of chromosomes #1, #6, #7, and #11 from 22 malignant melanoma direct tumor and cell line studies. These profiles are based on the combined clonal numeric and structural abnormalities described (see text for further discussion).

This analysis of the chromosomal data suggests that in melanoma the gain of an entire chromsome 7 as well as the loss of very specific regions of chromosomes 6q and 11p are most frequently gained or lost in this disorder.

This section has dealt with chromosome segments which appear nonrandomly altered in malignant melanoma. In the next three sections, a description of the most frequent chromosome alterations involving #1, #6, #7, #11, and #19 will be described.

Chromosomes 1 and 19

Chromosome 1

Chromosome 1 represents the most prevalent site of alteration in malignant melanoma, with ~85% of all tumors displaying numeric or structural alterations of this chromosome (particularly flanking the centromere) (Figure 2). However, despite the prevalence of chromosome 1 abnormalities in malignant melanoma, this frequency of alteration is by no means "specific" to melanoma. Chromosome 1 is in fact the single most frequent site of chromosome alterations in all human solid tumors, as well as in many different forms of human hematopoietic malignancies (7).

There has been long standing speculation that the high frequency of chromosome 1 alterations in malignant melanoma (and other tumors) is related somehow to the progression (rather than genesis) of malignancies (for review see 23). Although this hypothesis has not yet been experimentally verified, with the incredibly high frequency of chromosome 1 alterations essentially across all histologic subtypes, it remains tempting to speculate that a subset of genes on chromosome 1 (tumor suppressor genes?) will eventually be recognized which do play a general role in tumorigenesis.

Chromosome 19

As previously mentioned, alterations of chromosome 1, particularly those involving the long arm, are a frequent finding in many cancers including malignant melanoma. In contrast, structural alterations of chromosome 19 are much less common. Recently, Nowell and colleagues (17) described a nonreciprocal translocation involving chromosomes 1 and 19 [t(1;19)(q12;p13)] which appears to define a subset of patients with this disorder. The translocation breakpoint along chromosome 1 in the three patients described in this report involved the C-band positive (constitutive heterochromatic) region near the centromere of 1q; a region which is considered to have little (if any) genic activity. In

contrast, the region of chromosome 19 involved in this translocation appeared to occur close to the chromosomal loci of the gene for insulin receptor (INSR), a gene which shows considerable structural and sequence homology to the erb-B oncogene (as well as members of the src family) (30). Accordingly, there is speculation that a gene(s) residing at band region 19p13 might be important in melanoma carcinogenesis (17).

As can be observed in Figure 2, studies from the author's laboratory of 28 cases of malignant melanoma revealed no examples of structural alteration involving chromsome 19. However, despite the relative infrequency at which t(1;19) translocations are observed, the recognition of these types of recurring alterations will unquestionably be of significant future value. Specifically, as the cytogenetic profile of solid tumors becomes better defined, it will increasingly be possible to subdivide cancers (such as melanoma) into clinically definable subgroups (as cytogenetics has done successfully for the human leukemias). Accordingly, it will be of importance as further cases of t(1;19) are reported to document characteristic features of the biology, pathology, and clinical features characterizing these patients.

Chromosome 6

Next to chromosome 1, chromosome 6 is most consistently involved in structural abnormalities in malignant melanoma (Figure 2, Table 1). Although case reports of alterations involving the short arm have appeared (4), alterations of the long arm of 6 (6q) are by far most frequently reported in melanoma (Table 1). Alterations of 6q have principally included the deletion of the distal long arm of 6 (6q-) as well as translocations of several different chromosomes to 6q.

In regards to the simple deletion of chromosome 6q, the breakpoints do vary considerably between individual patients. However, the chromosome segment distal to band region 6q23 is invariably lost in these deletions. Of interest, the overwhelming majority of tumors with a 6q- continue to retain additional copies of apparently normal chromosome 6's.

A number of different chromosomes have been reported to participate in nonreciprocal translocations involving 6q (6,24,28), although until recently a recurring pattern to these translocations had not been described (Table 1). We recently reported a recurring translocation site involving band region 6q11-13, based on the chromosome banding profile of 28 new cases of direct or short term cultures of melanoma examined in our laboratory (29). We identified five cases of melanoma displaying translocations involving chromosomes 1 and 6 [t(1/6)]. The cytogenetic investigation revealed clonal chromosomal alterations in every tumor with no karyotypically normal cells observed. The most

striking feature in all of these tumors was the involvement of band region 6q11-13 in nonreciprocal translocations with chromosome 1. As illustrated in Figure 6, three cases exhibited nonreciprocal translocations between band regions 1q12 and 6q11-13 [t(1;6)(q12;q11-13)], while in one case either the proximal short arm (p22) or long arm (q21) of chromosome 1 was translocated to 6q11-13. In reviewing the published literature, additional two cases of this identical translocation have been identified, as well as the identification of additional 13 cases in which other chromosomes were translocated to the 6q11-13 band region (29) (Figure 7).

Importantly, the translocations described above were shown to be present in both established melanoma cell lines, and also in direct cultures of malignant melanomas (suggesting that this abnormality is not an artifact of in vitro culture).

In summary, a translocation site involving chromosome 6q has recently be recognized which characterizes seven cases of t(1;6) and an additional 13 cases in which other chromosomal regions have been translocated to 6q11-13. The involvement of 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.

It would appear from these studies that the translocation site involving 6q11-13 defines a region on chromosome 6q which is significantly removed (particularly at the nucleotide level) from those band regions frequently lost via chromosomal deletion (Figure 7). Although the cytologic location of the translocation site is distant to the most common area lost in 6q deletions, it appears possible that the deletion of sequences on 6q and the frequent occurrence of nonreciprocal translocations involving 6q may in fact be related. Specifically, while this translocation site may define the site of a gene(s) disregulated via this chromosome abnormality, it is also possible that the high frequency of nonreciprocal translocations in this region could in fact represent an alternate means of removing sequences on distal 6q [leading to the loss of heterozygosity (LOH)] (Figure 7). If this latter situation is correct, both the simple deletion as well as the nonreciprocal translocation of 6q would both provide the same end result, namely, the LOH of alleles on distal 6q. Using Southern blotting and polymorphic DNA probes, our laboratory has very recently documented the LOH of 6q alleles in at least a subset of patients with malignant melanoma. This area is receiving significant attention in our future investigations of this disorder.

Finally, in considering the possible importance of chromosome 6 to malignant melanoma, Figure 8 points out several biologically important gene sequences, including proto-oncogenes, which have been assigned to 6q (for review see 10,21). Furthermore, numerous cancers in addition to melanoma have

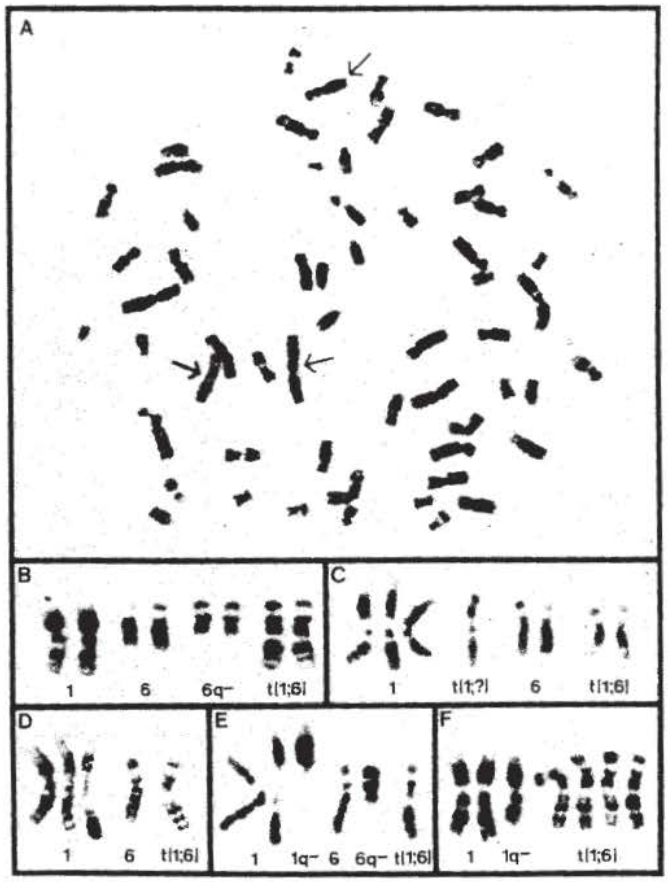

Figure 6: Representative examples of G-banded cells from five cases of melanoma displaying a translocation between chromosomes 1 and 6. Detailed description of chromosome breakpoints are provided in Table 1A. [A] G-banded metaphase of case T87-069. Thin arrows indicate a normal chromosome 1 and 6 for comparison with the t(1;6) (bold arrow). Normal and clonal structural abnormalities of the five identified cases of t(1;6). (From reference 22 with permission).

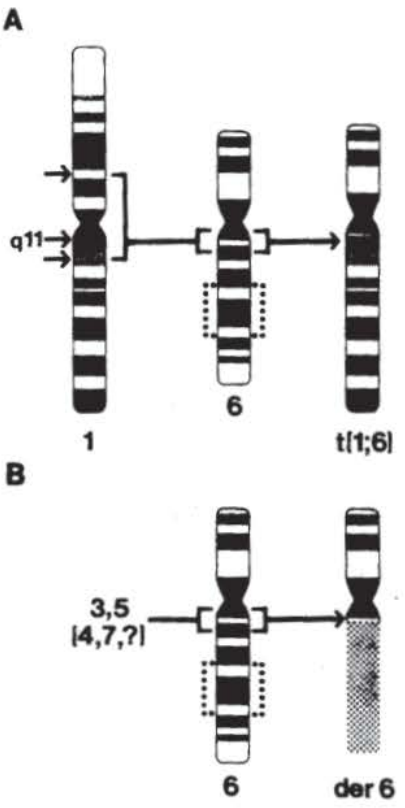

Figure 7: Idiogram diagramming breakpoints and derivative chromosomes resulting from translocations of various chromosomes to 6q11-13. [A] Breakpoints involving chromosomes 1 and 6 with resulting derivative t(1;6). Arrows to chromosome 1 indicate the different sites involved in translocation with 6q11-13 (solid brackets). [B] Chromosomes #3, #4, #5, #7, and unidentified chromosomal segments (?) were also shown to translocate to 6q11-13. The open brackets illustrate the region of 6q most frequently involved in simple deletions (see text). (From reference 22 with permission).

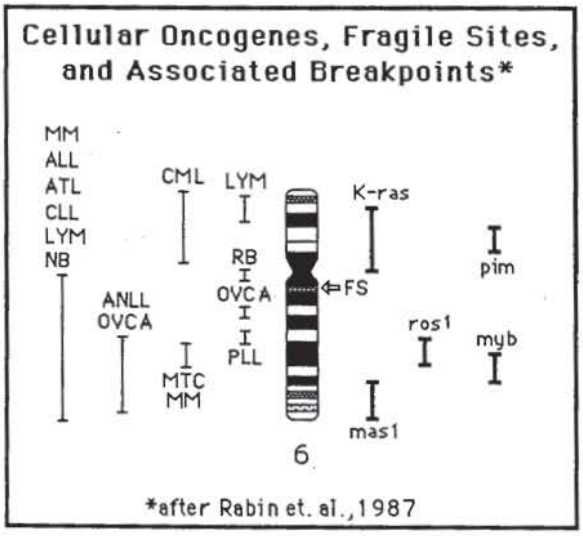

Figure 8: Idiogram of chromosome 6 indicating band regions of tumor associated breakpoints, known cellular oncogenes, and fragile sites (FS). The tumor types listed include: malignant melanomas (MM); ovarian carcinoma (OVCA); acute lymphocytic leukemia (ALL); adult T-cell leukemia (ATL); chronic lymphocytic leukemia (CLL); malignant lymphoma (lym); neuroblastoma (NB); acute nonlymphocytic leukemia (ANLL); mediastinal teratocarcinoma (MTC); and prolymphocytic leukemia (PLL). Abbreviations for cellular homologs of nontransforming retroviruses include: Kirsten murine sarcoma virus (K-ras); pim-1 murine leukemia virus-associated transforming gene (pim); and avian myeloblastosis virus transformating gene (myb). The ros-1 oncogene was cloned from DNA from MCF7 following transfection (and was originally designated MCF3). Strong homology (based upon nucleotide sequence) to the UR2 strain of avian sarcoma virus exists. Mas1 was isolated using co-transfection into NIH-3T3 and does not appear to have a homologous viral counterpart. The open arrow points to the site of a common FS at 6q13. Chromosome 6 also exhibits a heritable FS at 6p23, as well as constitutive FS's at 6p25, 6p22, and 6q26. (After ref. 21).

also been documented to display alterations of 6q (7). Unfortunately, almost no molecular studies of 6q rearrangements have appeared in the literature, although *c-myb* expression has been shown to be altered in a subset of leukemias containig structural chromosome alterations involving 6q (5). With the exception of rare case reports of *c-myb* rearrangements in melanoma cell lines (1), virtually no evidence for structural alterations of oncogene sequences mapping to 6q have been documented in this disorder. Additionally, to date, our own laboratory has failed to observe any structural alterations of *c-myb* in any direct specimen from 20 melanomas examined in our laboratory (using standard gel electrophoresis and Southern blotting). Studies are now underway in our laboratory using pulsed field gel electrophoresis to examine the possibility that structural gene alterations of the *myb* locus indeed occur in malignant melanoma but go unrecognized by standard Southern blotting.

Chromosomes 7 and 11

Chromosome 7

Chromosome 7, like chromosome 1, is among the most commonly altered chromosomes in human malignancies (7). However, the chromosome 7 abnormalities most frequently characterizing malignant melanoma are somewhat unique. First, as detailed previously, chromosome 7 is by far the chromosome most highly represented in malignant melanoma. Further, this increase is unique in that the additional segments of chromosome 7's result primarily from additions of normal homologs. However, when structural chromosome alterations are recognized, the area surrounding the centromere (7p12->7q11) appears most frequently to be involved. Both findings may be related to the observation that enhanced expression of the epidermal growth factor receptor (EGFR) gene (which maps to 7p12) is associated with an increased number of copies of chromosome 7p (13). Finally, it is also of interest that chromosome 7 stands in contrast to all other chromosomes by completely lacking any evidence of net loss of any portion of this chromosome (Figure 5).

Chromosome 11

Chromosome 11 alterations are also frequently observed in malignant melanoma, with approximately 70% of cases studied in our laboratory evidencing abnormalities of chromosome 11. In general, chromosome 11p (and particularly the terminal region most frequently involved in structural rearrangement. Recently,

Mitelman and colleagues (11) have reinforced the suggestion that chromosome 11p alterations may play a role in melanoma tumorigenesis. In this study, six cell lines from three melanoma patients were characterized cytogenetically with chromosome 11p alterations (primarily translocations) observed in each case.

In summary, alterations of 11p appear to vary significantly in regard to both the type of chromosome aberration (predominantly translocations and deletions) as well as the exact breakpoints along 11p involved. However, because the 11p13 locus has been implicated as a possible site of a tumor suppressor gene (14), testing of melanomas for LOH at this locus would appear worthwhile.

ONCOGENE LOCI IN RELATION TO RECURRING SITES OF CHROMOSOME CHANGE

Although significant attention has been focused on the role of oncogenes in the pathogenesis of human malignancies, unequivocal evidence directly involving a specific oncogene in melanoma tumorigenesis is still lacking. Even though the precise role of cellular oncogenes in human malignancies in general (and melanoma specifically) is still inexactly understood, available information on the chromosomal location of oncogenes in relation to tumor associated chromosomal breakpoints significantly supports a link between chromosome alterations, cellular oncogenes, and development of specific human cancers.

Figure 4 depicts those chromosomes most frequently altered in malignant melanoma and pinpoints the chromosomal location of selected cellular oncogenes. As can be observed, the chromosomal loci of several oncogenes lies within regions of chromosomes 1, 6, 7, 11, and 19 which are nonrandomly altered in melanoma. Unfortunately, at present we do not yet have convincing evidence to correlate any of the proposed sites of chromosome change in malignant melanoma with altered regulation of a specific cellular oncogene (1). The one possible exception is the aforementioned association of chromosome 7 abnormalities and altered expression of the EGFR gene (the homolog of the *c-erb-B* oncogene) (13). However, the study implicating chromosome 7 alterations as a mediator of enhanced EGFR expression was confined to the study of cell lines only, and curiously it was a simple numeric change (and not structural alteration of 7p) which most clearly correlated with enhanced EGFR expression (13).

While no clear association as yet exists between the sites of recurring chromosome change and the altered regulation of oncogene sequences, several laboratories are examining the

possibility that altered expression of cellular oncogenes will be a characteristic feature of malignant melanoma (for review see 10).

Finally, cytogenetic examination of human cancers has also been extremely helpful in indicating the presence of amplified cellular genes (including oncogenes) (2). Specifically, amplification of cellular genes is almost unfailingly associated with the cytologic correlate of double minutes (DMs) or homogeneously staining regions (HSRs) [the chromosomal manifestation of amplified genes]. Human tumors such as neuroblastoma, breast, lung, and brain cancers have frequently been shown to display DMs or HSRs, and subsequently have been shown to harbor amplification of cellular oncogenes (2). Although the number of reports of melanoma are reasonably limited, melanoma does not ordinarily evidence either DMs or HSRs and, not surprisingly, despite extensive analysis, no evidence for significant amplification of a previously recognized cellular oncogene has appeared in this cancer (10).

Summary

This review has provided an update on current progress in identifying recurring sites of chromosome change in human malignant melanoma. Despite methodologic difficulties, a recurring and decidedly nonrandom pattern of chromosome change is beginning to emerge for this neoplasia. It appears most reasonable to suggest that as an increasing number of cases of melanoma are cytogenetically examined, the stratification of patients into defined subgroups based upon specific chromosome abnormalities will be possible.

At present, the clinical utility of chromosome analysis in malignant melanoma is indeterminate. However, the pinpointing of regions of the genome which are characteristically altered in this tumor may be of significant benefit in targeting future molecular (and hopefully mechanistic) investigations. Continued study of the basic genetics of malignant melanoma would appear a particularly fruitful avenue to continue and it assuredly will add to our understanding of the causation, progression, and ultimately the control of this disorder.

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