Evidence for Three Tumor Suppressor Gene Loci on Chromosome 8p in Human Prostate Cancer

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ABSTRACT

Allelic loss of human chromosome sequences is often equated with inactivation of putative tumor suppressor genes. Loss of sequences on the short arm of chromosome 8 (8p) has been observed in human cancers, especially of 8p22 in prostate tumors. By using PCR analysis of highly polymorphic microsatellite repeat markers at nine 8p loci in 135 tumors, we observed deletion of sequences at 8p22 and at two other proximal deletion domains. These novel deletion domains encompass the NEFL locus and D8S87-ANK1 loci, respectively. These data suggest that three 8p tumor suppressor gene loci may be independently deleted in human prostate cancers.

INTRODUCTION

It is likely that many genetic and epigenetic events are involved in tumorigenesis. In particular, recent cytogenetic and molecular studies have suggested that deletion or rearrangement of sequences that map to the short arm of chromosome 8 may be permissive for tumorigenesis in several organ systems. Cytogenetic studies have described deletions or translocations involving 8p12 in adenocarcinomas of the colon, kidney, and breast and involving 8p21–23 in adenocarcinomas of the pancreas, stomach, colon, breast, and uterus (1). Molecular studies first described LOH(2) at 8p21 and 8p23 in 50% of colorectal carcinomas studied (2) and at 8p23–pter in 25% of pancreatic, 50% of gastric, and 50% of colorectal carcinomas (3). Subsequent work reported independent deletion of sequences at 8p23.2–p22 and at 8p21.3–11.2 in 30–40% of colorectal carcinomas (4); these findings were consistent with those of Cunningham et al. (5) who reported deletion of sequences within 8p22–8q11.2 in 51% of colorectal carcinomas analyzed (5). Deletion of 8pter–p21.1 and 8p12–22 sequences has been observed in breast carcinomas (6, 7), and deletion of 8p22–q11.2 has been observed in bladder carcinomas (8). LOH for sequences at 8p21.3–p22 has also been reported in hepatocellular (9) and lung (10) carcinomas. Taken together, these studies suggest that deletion of one or more 8p sequence domains may be permissive for tumorigenesis in several organ systems, perhaps due to the loss of putative tumor suppressor genes that map to those regions. Sequence deletions within the 8p chromosomal region have also been observed in prostate tumors. Cytogenetic studies reported by Lundgren et al. (11) cited alterations of 8p in 3 of 15 cases examined, involving regions 8p22, 8p21, or 8p11. Bergerheim et al. (12) observed loss of sequences on 8p in 65% of prostate tumors examined. Subsequent molecular genetic work has reported high frequencies of deletion involving the 8p22 chromosomal region in human prostate tumors (13–17) and less frequent deletion of more proximal sequences that map near 8p12 (16, 17). Taken together, these studies suggest that more than one tumor suppressor gene locus may be deleted in prostate cancers. To test this hypothesis, we have performed deletion analysis of nine 8p loci in 135 prostate tumors and, as described below, we have identified three independently deleted 8p sequence domains in human prostate tumors.

MATERIALS AND METHODS

Prostate tissue was obtained after radical prostatectomy from 135 patients diagnosed with prostate cancer. Tumor pathological stage, degree of differentiation (combined Gleason score), and the ethnic composition of the patient population are detailed in Table 1. PSA information comprising two or more consecutive serum PSA values taken at 3- or 6-month intervals postoperatively was available for 78 of the 135 patients. All PSA assays were performed in the same clinical laboratory (Harper Hospital, Detroit, MI). PSA values were considered undetectable at values ≤0.05 ng/ml. Rising PSA values were defined as two or more consecutive increases in value and both >0.05 ng/ml.

After pathological evaluation of radical prostatectomy tissue, frozen or paraffin-embedded tumor specimens comprising areas of at least 70% malignant cells and nontumor specimens comprising normal or hyperplastic epithelium were serially sectioned. One section was stained with hematoxylin and eosin to define areas of discrete histology. These areas were then excised from adjacent nonstained sections, and DNA was extracted as described previously (14, 15, 18, 19). PCR amplification assays targeted sequences containing highly polymorphic microsatellite repeat markers at loci of interest on 8p, including D8S201 (20), D8S252 (21), LPL (LPL-3'-CA and LPL-3'-GT primers) (22), D8S133 (23), NEFL (24), D8S37 (25), D8S87 (26), ANK1 (27), and PLAT (28). The linkage order of these markers has been established as: D8S201-D8S252-LPL-D8S133-NEFL-D8S37-D8S87-ANK1-PLAT (Ref. 21, 29; see Fig. 1). In addition, polymorphic microsatellite sequences at the FBW1 locus (12pter–p12) were amplified for use as unlinked dosage controls. For each PCR reaction, 5 μl of DNA were amplified in 20 μl of a mixture comprising 200 μM concentration of each dGTP, dATP, dTTP, and dCTP; 2.5 μCi [α-32P]dCTP (3000 Ci/mmol; NEN); 1 μM oligonucleotide primers; and 0.6 unit of Taq polymerase (GIBCO-BRL). The reactions were cycled at 95°C for 5 min (to completely denature template), then at 95°C for 1 min, 55°C (primer-dependent) for 1 min, and 72°C for 1 min for 35 cycles; 72°C for 7 min and a 4°C soak to stop reactions. Aliquots of each reaction were electrophoresed on 6% acrylamide-7 M urea sequencing gels, and the gels were autoradiographed. Allelic loss was scored when allelic signal intensities in tumor tissue were ≥50% of those for normal tissue from the same patient (14, 15, 18, 19). Statistical analysis was performed utilizing a χ2 (Fisher exact) test, with P values ≤0.05 considered statistically significant.

RESULTS

Tumor Histopathology and Patient Population

Specimens were collected from patients ages 39–79 years (mean age, 64.5 years) at the time of surgery who underwent radical pros-

Received 6/5/95; accepted 9/11/95.

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1 This work was supported in part by National Cancer Institute Grant R29 CA 06948 (J. A. M) and a Department of Veterans Affairs grant (J. A. M).

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3 The abbreviations used are: LOH, loss of heterozygosity; PSA, prostate-specific antigen; MS, microsatellite.


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Evaluation of 135 prostate tumors for deletions at nine chromosomal loci on 8p demonstrated loss of frequencies ranging from 7% at PLAT (6 of 80 informative tumors) to 30% for D8S133 (22 of 69 informative tumors; see Table 2). Fractional allelic loss for 8p loci was 62% (84 of 135), indicating that at least one 8p locus was deleted in 62% of tumors examined (see Table 1). Nonspecific (background) allelic loss was estimated by using deletion frequencies of the F8VWF locus on chromosome 12p, which equaled 6% (5 of 88 informative tumors). Deletion frequencies at the LPL (P = 0.002), D8S133 (P < 0.0001), NEFL (P < 0.0001), D8S87 (P = 0.002), and ANK1 (P = 0.025) loci were statistically significantly different from background frequencies; frequencies at the D8S201, D8S252, D8S137, and PLAT loci were not. This information distinguished loci LPL, D8S133, NEFL, D8S87, and ANK1 as important regions of deletion in prostate tumors. Homozygous deletion appeared to occur in five tumors for the D8S133 and NEFL loci; however, efforts to verify these results by using multiplex PCR analysis were inconsistent.

**Identification of Three Deletion Domains on 8p**

Observation of allelic loss or retention frequencies at individual loci in prostate tumors identified three potential 8p deletion domains. These comprise the LPL-D8S133 loci (group 1 tumors), NEFL locus (group 2 tumors), and D8S87-ANK1 loci (group 3 tumors).

**Group 1 Tumors.** Twenty-five tumors were deleted at LPL and 22 were deleted at D8S133 (Table 2). Of these, 6 tumors were deleted at both loci, 19 were deleted only at LPL, and 16 were deleted only at D8S133. Thus, 41 of 84 tumors with deletions on 8p were deleted at LPL-D8S133. More than one-half of these tumors, 23 of 41 or 56%, were deleted only or primarily at LPL and/or D8S133, with retention of adjacent, flanking informative loci (D8S201 or D8S252 distally and NEFL proximally; Table 1). The retention of proximal and distal flanking loci and the high frequency of allelic loss involving LPL and/or D8S133 suggests that LPL-D8S133 may be part of a deletion domain. Tumors with deletions primarily or only at LPL-D8S133 have been classified as group 1 tumors (Table 1). Allelic loss or retention patterns for 7 of the 23 group 1 tumors are shown schematically in Fig. 1, including tumors with deletions in LPL (cases 149 and 446), D8S133 (cases 171, 311, and 414), and LPL-D8S133 (cases 168 and 313). Gel autoradiographs for case 446 are shown in Fig. 2A. The frequency of LPL-D8S133 allelic losses was significantly different

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**Table 1 Summary of 8p allelic loss in 135 prostate tumors**

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<th>Category</th>
<th>LN&lt;sup&gt;a&lt;/sup&gt;</th>
<th>SV</th>
<th>EPE</th>
<th>LOC</th>
<th>Total</th>
<th>Combined Gleason score&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PSA&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>2 (8)</td>
<td>8 (24)</td>
<td>4 (21)</td>
<td>1 (6)</td>
<td>8 (20)</td>
<td>23 (17)</td>
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<td>4 (8)</td>
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<td>4 (9)</td>
<td>2 (11)</td>
<td>3 (19)</td>
<td>6 (15)</td>
<td>19 (14)</td>
<td>7 (14)</td>
<td>9 (14)</td>
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<td>Group 4 FAL</td>
<td>7 (27)</td>
<td>3 (12)</td>
<td>4 (21)</td>
<td>2 (13)</td>
<td>3 (7)</td>
<td>19 (14)</td>
<td>8 (16)</td>
<td>8 (13)</td>
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<td>Total 8p FAL</td>
<td>17 (65)</td>
<td>16 (48)</td>
<td>10 (53)</td>
<td>9 (57)</td>
<td>21 (52)</td>
<td>73 (54)</td>
<td>26 (52)</td>
<td>37 (59)</td>
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<td>7 (27)</td>
<td>14 (43)</td>
<td>7 (36)</td>
<td>6 (37)</td>
<td>17 (41)</td>
<td>51 (38)</td>
<td>17 (38)</td>
<td>21 (33)</td>
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<tr>
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<td>33</td>
<td>19</td>
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<sup>a</sup>Shown are the number of tumors and the percentage of tumors with fractional allelic loss (in parentheses).
<sup>b</sup>LN, metastatic to regional lymph nodes; SV, invasive to seminal vesicles; EPE, extraprostatic extension through prostatic capsule; LOC, localized to the prostate; R, rising PSA; U, undetectable PSA.
<sup>c</sup>FAL, fractional allelic loss (number of tumors with allelic loss/total number of informative tumors).
<sup>d</sup>AAM, African-American men; CM, Caucasian men.

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Fig. 1. Schematic representation of allelic loss and retention of patterns for nine 8p loci in prostate tumors. Left, ideogram of 8p chromosomal region showing map locations of the nine loci. The loci are arranged in their linkage order from 8pter-centromere. Right, schema of allelic loss distributions in selected tumors. ©, both alleles retained; ●, allelic loss; —, not informative; ×, instability; blank area, not determined. Boxes demarcate loci within the three major regions of deletion: LPL-D8S133, group 1 tumors; NEFL, group 2 tumors; D8S87-ANK1, group 3 tumors. Group 4 tumors have deletions in two or more deletion domains.

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Group 2 Tumors. Twenty-two tumors were deleted at the NEFL locus (see Table 2). Of these, over one-half (12 of 22, 55%) were deleted only or primarily at NEFL, with retention of adjacent flanking loci (D8S133 distally and D8S137 proximally; Table 1). The moderate frequency of allelic loss involving NEFL and the retention of proximal and distal flanking loci suggest that NEFL may lie within a deletion domain. Tumors with sole or primary deletions at NEFL have been designated as group 2 tumors (Table 1). All tumors or retention patterns for 4 of the 12 group 2 tumors are shown schematically in Fig. 1 (cases 207, 219, 353, and 374). Gel autoradiographs for case 207 are shown in Fig. 2B. The frequency of NEFL allelic loss was significantly different from that of proximal locus D8S137 (P = 0.033) but not from that of distal locus D8S137 (Table 2).

Group 3 Tumors. Of 84 tumors with deletions on 8p, 20 were deleted at the D8S87 locus, 19 were deleted at the ANK1 locus, and 3 were deleted at both loci. Of these, almost one-half (19 of 42, 45%) were deleted only or primarily at D8S87 and/or ANK1, with retention of adjacent flanking loci (D8S137 distally and PLAT proximally; Table 1). The retention of proximal and distal flanking loci, together with the high frequency of allelic loss involving D8S87-ANK1, suggests that these loci may be part of a deletion domain. Tumors with sole or primary deletions at D8S87-ANK1 are designated group 3 tumors (Table 1). Allelic loss or retention patterns for 5 of the 19 group 3 tumors are shown schematically in Fig. 1, including tumors with deletions at D8S87 (case 230), ANK1 (cases 361, 435, and 438), and D8S87-ANK1 (case 303). Gel autoradiographs for case 230 are shown in Fig. 2C. The frequency of D8S87-ANK1 allelic loss was significantly different from that of proximal locus D8S137 (P = 0.048) and distal locus PLAT (P = 0.033; Table 2).

Group 4 Tumors. Although groups 1, 2, and 3 tumors were characterized by deletions primarily at LPL-D8S133, NEFL, or D8S87-ANK1, other tumors were characterized by deletions involving two or more of these regions. These tumors are referred to as group 4 tumors and comprise 19 of 84 (23%) of all tumors with 8p deletions (Table 1). Of the 19 group 4 tumors, 2 were deleted for LPL-D8S133 and NEFL, 9 were deleted for LPL-D8S133 and D8S87-ANK1, 1 was deleted for NEFL and D8S87-ANK1, and 7 were deleted for all three domains. None of the group 4 (or any) tumors demonstrated deletion of all informative loci on 8p. Allelic loss or retention patterns for 6 of the 19 group 4 tumors are shown schematically in Fig. 1, 2, with deletions at LPL-D8S133 and NEFL (cases 205 and 370); two with deletions at LPL-D8S133 and D8S87-ANK1 (cases 159 and 291), and two with deletions at all three domains (cases 145 and 448). Gel autoradiographs of case 448 are shown in Fig. 2D.

The deletion frequency for total allelic losses within LPL-D8S133, NEFL, and D8S87-ANK1 was significantly higher than background (73 of 135 tumors; P < 0.0001), as was the frequency for all 8p loci (84 of 135 tumors; P < 0.0001). Allelic loss frequencies for the three deletion domains were not statistically different from each other for all tumors combined (Table 1).

Correlation of 8p Allelic Loss with Tumor Stage and Grade

Deletion frequencies for LPL-D8S133, NEFL, and D8S87-ANK1 or for all 8p loci, were not significantly different between metastatic and localized prostate cancers. Both metastatic and localized cancers exhibited high frequencies of loss of 8p sequences (59% in localized and 73% in metastatic tumors). The majority of deletions (>90%) involved sequences within the three deletion domains.

Grades 7—9 tumors demonstrated significant frequencies of deletion within LPL-D8S133 (P = 0.011), although grades 4—6 tumors did not (Table 1). This suggests that tumors with at least one poorly differentiated component (equivalent to combined Gleason scores of 7—10) are characterized by similar degrees of deletion for LPL-D8S133. Overall frequencies of allelic loss, whether restricted to the three deletion domains or inclusive of all 8p loci, were not significantly different between poorly (grades 7—9) and moderately (grades 4—6) differentiated tumors. Total 8p allelic loss frequencies ranged from 26% in grades 4—6 to 67% in grade 7 and 62% in grades 8 and 9 tumors, suggesting that (a) all tumors demonstrated high frequencies of loss; and (b) grade 7 tumors were more similar to grades 8 and 9 tumors than grades 4—6 tumors in frequencies of loss.

Correlation of 8p Allelic Loss with Postprostatectomy PSA Levels

At least two consecutive (at 3- or 6-month intervals) postprostatectomy serum PSA levels were available for 78 of 135 patients evaluated in this study. PSA levels were considered undetectable at levels of ≤0.05 ng/ml or rising at increasing values >0.05 ng/ml for at least two consecutive readings. Seven patients that demonstrated deletion at loci other than LPL-D8S133, NEFL, or ANK1-D8S87 also exhibited rising PSA values. Five were deleted for sequences proximal to the three deletion domains, at loci D8S201 and D8S252, whereas none of the patients with undetectable PSA values demonstrated deletions at these two loci (P = 0.024). No significant differences in fractional allelic loss frequencies among the three deletion domains, or for total 8p loss, were observed in tumors between patients with undetectable or rising PSA values. It should be noted, however, that these trends reflect data from only a subset (78 of 135) of the tumors examined.
Correlation of 8p Allelic Loss with Patient Ethnic Origin

The distribution of tumor pathological stage and grade was similar between the two major ethnic groups analyzed, African-American and Caucasian (Table 1). Thus, tumors from the two ethnic groups can be considered stage and grade matched. Within the 135-member patient population, 63 were African-American men, 64 were Caucasian men, and 8 men were of unknown ethnic origin. No significant differences in fractional allelic loss frequencies among the three deletion domains, or for total 8p loss, were observed between African-American men and Caucasian men. With regard to loss differences between individual 8p loci, however, some trends were evident. For example, 5 of 6 (83%) deletions at the D8S201 locus were observed in tumors from African-American patients. Conversely, higher frequencies of loss at the D8S252 (7 of 10), PLAT (5 of 7), and ANK1 (11 of 19) were observed in tumors from Caucasian men than African-American men (Table 2). The locus ANK1, part of the D8S87-ANK1 deletion domain,
was deleted at a 2.5-fold higher frequency in tumors from Caucasian compared to African-American men (Table 1). It should be noted, however, that these trends reflect data from a small number of tumors and are not statistically significant.

**Microsatellite Instability in Prostate Tumors**

Microsatellite instability, used as an indicator of the replication error repair- or defective in mismatch repair-phenotype, was observed once at the D8S201, NEFL, D8S137, and D8S87 loci, twice at D8S252, and four times at the D8S133 locus, for a total instability frequency of 10 of 135 or 7%. No tumors demonstrated evidence of microsatellite instability at more than one locus. Nine of the ten tumors were grades 7—9 and one was grade 6. This suggests that the replication error repair phenotype may not be characteristic of prostate cancers and that it occurs primarily in poorly differentiated tumors.

**DISCUSSION**

In this study, we have identified three distinct regions of interstitial deletion on chromosome 8p in human prostate cancers. Deletion analysis of nine loci on 8p in 135 prostate tumors demonstrated specific deletion of these regions with retention of adjacent, flanking loci.

The first region, LPL-D8S133, encompasses a 6.1-cM region (21, 29). This was the most frequently deleted domain, lost in all groups 1 and 4 tumors, and characterized almost one-half (41 of 84) of the loss in tumors with 8p deletions (Table 1). Many tumors (23 of 84 or 27%) with 8p losses were deleted only at LPL-D8S133 with retention of proximal (D8S201 and D8S252) or distal (NEFL-PLAT) loci. LPL-D8S133 lies within the large distal 8p region deleted in prostate cancers initially identified by Bergerheim et al. (12). It is also part of a 14-cM region spanning loci D8S163-LPL described by Bova et al. (13), a 15-cM region including loci D8S206-D8S259 identified by MacGrogan et al. (16) and a 17-cM region spanning loci D8S133-D8S87 described by Trapman et al. (30), all frequently deleted in prostate cancers. It also lies within the larger 8p21.3–8p22 region reported as deleted in colorectal cancers (4) and the 8p22–21.3 region described as deleted in hepatocellular (9) and non-small cell lung (10) cancers. This information suggests that LPL-D8S133 lies within the major region of allelic deletion delineated in human prostate and other cancers.

The second region, defined by the NEFL locus, was the third most frequently deleted site, lost in all 12 group 2 and 10 of 19 group 4 tumors, e.g., in 22 of 84 or 26% of tumors with 8p deletions. A number of tumors (12 of 84 or 14%) with 8p sequence losses were deleted only at NEFL, with retention of adjacent flanking loci (LPL-D8S133 proximally and D8S137 distally). This site was considered the breakpoint region delimiting a large distal 8p deletion unit in the study by Bergerheim et al. (12). Our study shows that this large distal 8p deletion unit consists of two separate deletion domains, LPL-D8S133 and a distinct region including NEFL, that can be deleted independently of each other in prostate cancers. The NEFL locus has not been considered previously to lie within an independent deletion domain separate from other 8p deletion domains in prostate cancers. For example, Bova et al. (13) did not find the NEFL locus to be part of the major region or a separate region of deletion on 8p, although that study examined only six tumors at that locus. MacGrogan et al. (16) included the NEFL locus within a major region of deletion on 8p that also included the LPL locus and did not report independent deletion of LPL and NEFL in the tumors examined. Their criteria of defining LOH as at least a 30% loss of signal intensity (by using phosphomager quantitation and calculation of allelic imbalance ratios), however, is less stringent than the 50% loss criteria used in our study. It is, therefore, difficult to assess how the results of that study compare to those reported here. Finally, Trapman et al. (30) defined a region extending distally from D8S133 to D8S87 proximally that encompassed the NEFL locus, although they did not actually examine deletion frequencies at NEFL itself. This region includes portions of the three deletion domains defined in the present study. Beside the data reported in the current study, independent deletion of NEFL has been reported in breast carcinomas (7).

The third area, D8S87-ANK1, encompasses a 5.2-cM region (21, 29). This was the second most frequently deleted region, lost in all 19 group 3 and 17 of 19 group 4 tumors, and defines 42% (35 of 84) of loss in tumors with 8p deletions (Table 1; note that the percentage of loss of the 3 deletion domains calculated above for 84 tumors with 8p loss exceeds 100% because of loss of more than 1 domain in 19 tumors). Many tumors (19 of 84 or 23%) with 8p sequence losses were deleted only for D8S87-ANK1, with retention of distal (D8S137) and proximal (PLAT) loci. Other reports have noted deletion in this region, including MacGrogan et al. (16) and Trapman et al. (30). It is of interest that these two studies report very different loss frequencies for the distal locus flanking this region, D8S137: 18% (7 of 38 informative tumors; Ref. 16) and 69% (16 of 23 informative tumors; Ref. 30). The low frequency of deletion at D8S137 observed in the current study (8%, 5 of 63 informative tumors) is most similar to that reported by MacGrogan et al. (16) and is consistent with the existence of separate distal (NEFL) and proximal (D8S87-ANK1) 8p deletion domains. Additional evidence for the existence of a proximal region of deletion on 8p is provided in the current study and in the observation by MacGrogan et al. (16) of independent loss of ANK1 (although not of D8S87) in a small number of tumors.

The current study also observed high frequencies of 8p loss (primarily in the three deletion domains) in localized and moderately differentiated, as well as invasive and poorly differentiated tumors. Although a trend toward higher frequencies of 8p losses was observed in more advanced tumors, e.g., 59% of localized and 46% of moderately differentiated tumors compared to 70% of metastatic and 66% of poorly differentiated tumors, it is clear that a large proportion of less advanced tumors have sequence deletions on 8p. This suggests that allelic loss of 8p sequences may be “early” rather than “late” proportional events during prostate tumorigenesis.

Although trends toward higher 8p loss frequencies were observed in advanced compared to less advanced disease, allelic loss frequencies were not significantly different between tumors from patients with rising versus undetectable postoperative serum PSA levels within the three deletion domains or on 8p overall. If rising postoperative serum PSA levels may be taken as indicators of recurrent disease (31), the lack of association between 8p loss frequencies and rising PSA levels suggest that 8p sequence losses within the three deletion domains described here are not useful markers of recurrent disease. It is of interest that a significantly higher frequency of deletional events involving only distal 8p sequences (D8S201 and D8S252) was observed in tumors from patients with rising postoperative serum PSA levels (see Table 1). This suggests that deletion of some loci outside the three deletion domains on 8p may be important for the development of aggressive, recurrent tumors. Alternatively, other events on chromosome 8, e.g., gain of 8q, may be associated with prostate cancer recurrence (17). Studies using additional polymorphic markers and other molecular techniques (e.g., fluorescence in situ hybridization) should further define the 8p deletion domains and should show whether differential losses of 8p sequences or other chromosome 8 alterations have specific consequences for prostate tumor progression and outcome.
ACKNOWLEDGMENTS

The authors would like to thank Drs. Kenneth Plonta, Kathleen Cooney, and Sofia Merajver for their careful reading of the manuscript.

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