Allelic Imbalance and Microsatellite Instability in Prostatic Adenocarcinoma


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ABSTRACT

Although prostate cancer is one of the most common malignancies of males in Western countries, relatively little is known about the molecular mechanisms involved in tumor initiation and progression. Allelic loss studies have suggested the involvement of multiple tumor suppressor genes (TSGs), but few detailed studies of all chromosomes have been performed. In an effort to localize and identify candidate TSGs, we performed allelic imbalance (AI) studies on 55 prostate cancers, using 135 polymorphic microsatellite markers. For the entire chromosome, AI ranged from a low of 0% on chromosomes 14 and 20 to a high of 71% on chromosome 8. Chromosomal regions demonstrating at least twice the background frequency of AI (ranging from 20 to 69%) included 5q, 6q, 7q, 8p, 13, 16q, 18q, and 21. In addition, AI was examined for association with a number of clinicopathological parameters. AI on chromosomes 7 and 16 were each associated with greater age at diagnosis (P = 0.009 and 0.001, respectively), and AI on chromosomes 10, 16, and 18 was associated with aneuploidy/haploidyploidy (P = 0.037, 0.013, and 0.054, respectively). Furthermore, AI on chromosome 5 was associated with a higher pathological stage (P = 0.021) and on chromosome 8 and 16 with a higher Gleason score (P = 0.027 and 0.041, respectively). No tumor exhibited a phenotype of widespread microsatellite instability. These results indicate that there likely exist multiple sites harboring candidate TSG in prostate cancer, some of which may have important clinical implications, and which argue against widespread microsatellite instability.

INTRODUCTION

Prostate cancer is one of the most common malignancies of males in Western countries, accounting for 41% of all male cancers and 14% of male cancer-related deaths (1), with an estimated lifetime incidence of about 19% (1–5). Despite the high level of morbidity and mortality associated with this disease, very little is known about the molecular mechanisms involved in tumor initiation and progression. In recent years, substantial progress has been made in predicting outcome of patients with early prostate cancer. Currently, the most important prognostic factors appear to be stage, grade, ploidy, and tumor volume (6). In spite of these advances, however, the predictive ability of these factors for an individual patient remains limited, and new prognostic markers are needed to more precisely identify patients at risk for tumor recurrence and death.

The biology of prostate cancer is still poorly understood, but recent advances in our understanding of the molecular genetics of other common malignancies offer new insights that can be applied to the study of prostate cancer. Current evidence suggests that the process of tumorigenesis involves: (a) activation of dominantly acting oncogenes that promote cell proliferation (7); (b) the loss of TSG4 functions that normally regulate cell proliferation (8); and (c) mutator gene defects, such as the recently described alterations in several DNA mismatch repair genes (9–11). The role of TSGs in prostate cancer has been explored by AI and direct examination of known TSGs. Although there is a great deal of variability between studies, the cumulative data demonstrate frequent AI on chromosomes 7, 8, 10, 13, 16, 17, and 18 (12–41). Only one study has described a complete “allelotype” (20), with the highest frequency of allele loss occurring for chromosomes 8, 10, 16, and 18. Allelic loss at other chromosomal loci occurred at a lower frequency of 5–20%. The major limitations of that study, however, were that a limited number of DNA markers were available for each of the chromosomes examined, and the number of tumors examined was small. Two recent studies, using comparative genomic hybridization, reported loss on chromosome arms 8p, 13q, 6q, 16q, 18q, and 9p (27, 28).

Several chromosomes have exhibited the presence of AI, but most fine mapping studies have focused primarily on chromosome arm 8p (which has consistently shown the highest frequency of AI), 7q, and chromosomes 10 and 16. For chromosome 8, at least two regions have been implicated: 8p22 and 8p12-21 (29–36), and Macoska et al. (36) suggest an additional site. Allelic loss has been identified on both arms of chromosome 10 (19, 21, 25), and a recent report found a high rate of loss at 10q23-25 (37). A potential TSG mapped to 10q25, Mixl, seems not to be a gene important for the pathogenesis of prostate cancer (37). One region on chromosome 16 (16q22.1-24) is lost frequently (21), and the common region of deletion for chromosome 7 is 7q31.1-q31.2 (38–40).

The demonstration of AI for certain chromosomes has implicated previously identified TSGs, including APC on 5q, RB on 13q, p53 on 17p, DCC on 18q, and BRCA1 on 17q. Current data, however, suggest that p53 and RB do not appear to play a role in a significant number of prostate tumors, but rather are restricted to a subset of more advanced cases (12–14). Loss on chromosome 5q included the APC locus, but APC gene mutations are not always present (15). Similarly, the losses reported for the chromosome 17q and 18q arms include the regions to which BRCA1 (16, 17) and DCC (18) map, respectively. However, their role in prostate cancer remains unclear.

In an effort to delineate further the role of TSGs in prostate cancer, we performed AI studies on 55 prostate cancers using 135 markers, with approximately 6 markers for each chromosome (3 markers on acrocentric chromosomes). The data were analyzed to determine common regions of loss for some chromosomes and for any association with routine clinicopathological parameters.

MATERIALS AND METHODS

Tissue Samples. Paired prostate cancer and adjacent normal prostate tissues were obtained from patients undergoing radical prostatectomy at the Mayo Clinic between 1992 and 1994. Those portions not required for diagnostic purposes were immediately frozen at −70°C for future studies. The location, size, Gleason score, and pathologic stage of each cancer were recorded. As part of the routine clinical practice, DNA ploidy results from flow cytometric evaluation of paraffin-embedded sections were available (42).

DNA Extraction. Tissue processing and DNA extraction were performed as described previously (43). Briefly, using H&E-stained cryostat sections as reference, normal tissue was trimmed by microdissection of the specimen and...
DNA extracted from multiple 10-μm sections containing >70% tumor cells. Because of the nature of prostate cancer, it was not possible to entirely eliminate contaminating normal cells. DNA was also extracted from paired noncancerous tissue.

Microsatellite Analysis. We used 135 polymorphic microsatellite markers to examine chromosomes 1–22, with an average of 6 markers for each chromosome and 3 on the acrocentric chromosomes. PCR and gel electrophoresis were performed as described by Thibodeau et al. (11). Autoradiographs of normal/tumor pairs were analyzed by densitometry using NIH Image 1.47 software. AI was considered to be present when the relative intensities of the two alleles in tumor DNA differed from that present in the normal DNA lane by a factor of at least 1.5 (29). Although not all experiments were repeated, select samples (those with high frequencies of AI) were subjected to verification, and these showed good reproducibility. In general, normal DNA gave reproducible band intensities from run to run, although some variability was encountered. In a separate series of experiments, in which replicate PCR reactions were evaluated, replicate values for the ratio of allele bands varied typically by a difference of approximately 0–25%. For this reason, the difference between intensities had to exceed 1.5 to score a normal/tumor pair as having AI. Complete loss of an allele was relatively rare, because most prostate cancer DNA preparations contain DNA from contaminating nonmalignant cells.

Microsatellite instability at a given locus was defined by the presence of novel fragments after PCR amplification of tumor DNA that were not present in the PCR product generated by normal DNA (11).

Statistical Analysis. AI at each of the loci was assessed for associations with each of the following clinical and pathological parameters: patient age at diagnosis, preoperative PSA concentrations, pathological stage, Gleason scores, and DNA ploidy status. Fisher’s exact test was used for Gleason scores and when the sample sizes were insufficient for χ² analyses. The Mantel-Haenszel χ² test for linear trend was used to determine whether there was a trend in the proportions of AI over the levels of stage (44). The distribution of age at diagnosis was compared using the Wilcoxon rank sum test. All analyses were performed using the SAS software. Because of the difficulty in assessing the dependency of various parameters, none of the reported P values are corrected for multiple testing.

RESULTS

Patient Population. Matched normal and malignant tissues were obtained from 55 patients with prostate cancer. The clinicopathological parameters of these patients and their tumors are shown in Table 1.

AI. Using 135 microsatellite markers, chromosomal AI was examined for all autosomes in 55 prostate cancers. Examples of AI at selected markers are shown in Fig. 1. The markers were chosen from the telomeric, central, and centromeric regions of each chromosomal arm. Those selected for study and their chromosomal location are shown in Fig. 2. The order shown on the chromosomal ideogram represents the genetic order for each marker and, if known, its physical location. These data were obtained from current published genetic maps, and at this time, three markers (Fig. 2, *) cannot be placed at specific regions on the designated chromosome. Fig. 2 also shows the frequency of AI for each individual locus, and Fig. 3 shows the cumulative frequency of AI for each chromosome and chromosomal arm. The data for chromosome 7 were reported previously (38).

All but five tumors (91%) exhibited AI on at least one chromosome. AI on three or more chromosomes was noted in 35 (62.6%) tumors, although no specific combinations of chromosomal imbalance could be discerned. Chromosome 8 demonstrated the highest frequency of AI (71%), and the chromosome or chromosomal arm exhibiting the most frequent AI was at 8p (69%). In addition to chromosome 8, significant AI (≥20%) was found for chromosomes 1, 4, 5, 6, 7, 9, 10, 13, 16, 17, 18, and 21 (Fig. 3). When each of the markers was evaluated individually, however, AI on chromosome 1, 4, and 9 did not appear to preferentially involve any particular region (Fig. 2). Those areas suggesting particular regions of interest for AI include 3p25-26 (includes von Hippel Lindau gene), 5q12–q23 (includes APC), 6q, 7q31.1, 8p, 10q23-25, 13, 16q, 17p (includes p53), 18, and 21q22.2–q22.3.

Fig. 4 contains the data for those chromosomes exhibiting the highest frequencies of AI, namely, chromosomes 8, 16, and 18. For
### Genetic Changes in Prostate Cancer

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**Fig. 2.** Ideograms showing locations of microsatellite markers and frequency of AI for chromosomes 1–22. The order shown represents the genetic order for each marker. Boxes, regions demonstrating high rates of AI. * markers that cannot be placed at specific regions on the chromosome.

**Fig. 3.** The frequency of AI on the p arm (D), q arm (C) and whole chromosome (E) for each chromosome examined.

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chromosome 8, all but one of the tumors with AI on 8p exhibited AI at 8p22 loci. The highest frequency was at the Lipoprotein Lipase gene locus (Figs. 2 and 4), although six tumors did not show AI at this locus. Of the tumors not showing AI on chromosome 8 (n = 16), all but three were uninformative at one or more 8p22 loci. The two tumors without AI at 8p loci exhibited AI at D8S567, which maps...
distal to D8S87 and proximal to D8S164, and at D8S272, which maps to the telomeric region of 8q (8q24.2–q24.3).

For chromosome 18, D18S851 (18q21.1) exhibited the highest frequency of AI. AI at D18S64 (18q21.3) was also frequent, but DCC, which lies close to D18S851 at 18q21.1, was not often found to exhibit AI. One tumor exhibited imbalance at only D18S851; the other tumors with AI at D18S851 were either uninformative or had AI at D18S64 and/or DCC. For chromosome 16, AI was noted most frequently at D16S539 (16q24); only one tumor with AI on chromosome 16 did not show AI at this marker.

Microsatellite Instability. None of the cancers demonstrated widespread microsatellite instability. Eighteen tumors had alterations at one or two loci. Of the 5803 genotypes, microsatellite instability was detected at only 22. Changes were observed in both dinucleotide (14 of 22) and tetranucleotide (8 of 22) repeats. Compared to other cancers (such as colorectal carcinoma), the overall mutation rate observed at these loci in prostate cancer was extremely low.

Correlation of AI with Clinicopathological Parameters. For those chromosomes demonstrating significant rates of AI (chromosomes 5, 6, 7, 8, 10, 13, 16, 17, 18, and 21), the relationships between AI on a given chromosome or chromosomal arm and tumor DNA ploidy, pathological stage, and preoperative PSA concentration (Table 2), and patient age at diagnosis were examined. For these analyses, the chromosome or chromosomal arm was scored as having AI if any one
of the markers demonstrated AI on that chromosome or chromosomal arm. Survival analyses were not performed, because the follow-up times were limited and none of the patients had died. AI on chromosomes 10, 16q, and 18 (but not 18q alone) was associated with tumor DNA aneuploidy/tetraploidy (P = 0.037, 0.013, and 0.054 respectively; Table 2). There was no tendency for the seven aneuploid tumors to show AI on entire chromosomes. With the exception of chromosome 5, there was no association between AI and pathological stage for any of the chromosomes or chromosomal arms examined, either by examining for trends across all stages (Table 2) or by comparing nodal-positive versus nodal-negative cases (data not shown). Tumors showing AI on chromosome 5 were of higher stage than those without AI (P = 0.021; Table 2), with cancers from nodal-negative patients having more frequent AI, compared to those that were nodal-negative (P = 0.013, Fisher’s exact test). AI on chromosomes 8 and 16 (but not 16q alone) was associated with higher Gleason scores (P = 0.03 for both 8 and 8p, 0.04 for 16, and 0.12 for 16q; Table 2), whereas preoperative PSA levels showed a trend with AI on chromosome 8, but not 8p alone (P = 0.074 and 0.155 respectively; Table 2). Patient age at diagnosis was greater in patients whose tumors had AI on chromosomes 7 and 16, with the median ages of 69 for each, compared to 61.5 years each for those without AI (P = 0.009 and 0.001, respectively). No other associations were noted.

We next examined whether AI at specific loci or regions was associated with any of the above parameters. Although no associations were found for either the entire chromosome or the q arm of 7, AI at 7q31 was associated with higher Gleason scores as reported previously (P = 0.048, Fisher’s exact test; Ref. 38). None of the loci on chromosomes 6, 13, 16, 17, 18, or 21 showed association of AI with any of the parameters tested. For chromosome 5, however, AI at DSS5806 was marginally significant for an association with pathological stage (P = 0.062), although this was not the case for DSS5346 (APC); (P = 0.092). On chromosome 8, AI at D8S254 was associated with a higher Gleason score (P = 0.045), whereas D10S254 on chromosome 10 was marginally associated with ploidy (P = 0.071).

In addition to evaluating AI on each chromosome, we examined the cumulative number of chromosomes demonstrating AI in a tumor. This cumulative loss was evaluated in two ways: (a) the total number of chromosomes demonstrating any AI; and (b) the cumulative number of chromosomes demonstrating high frequency of AI (i.e., >20%). There was no association between the cumulative changes and pathological staging or Gleason scores. Tumors that were aneuploid or tetraploid had AI on an average of 4.6 chromosomes, whereas diploid tumors had AI on an average of 2.8 chromosomes (P = 0.0083). When only those chromosomes with high frequencies of AI were considered, a similar trend was noted (P = 0.006). Likewise, tumors from patients with preoperative PSA levels ≥10 ng/ml had AI on an average of four chromosomes compared with three chromosomes for those with PSA levels <10 ng/ml (P = 0.04). This association, however, was no longer statistically significant when only the chromosomes with high frequencies of AI were considered (P = 0.114).

### DISCUSSION

In this study, we performed a detailed allelotyping of 55 prostate adenocarcinomas with 135 highly polymorphic microsatellite markers. Those regions demonstrating the highest frequency of AI included 8p and 16q, followed by 18q, 6q, 7q, 5q, 21, 10q, 17p, 13, and 3p. Overall, these results are consistent with those published previously. As in other reports (29–36), chromosome 8 demonstrated the highest frequency of AI. In our study, 71% of tumors were found to have AI on 8 and 69% on 8p. Frequencies of AI, comparable to those reported previously, were detected for chromosomes 5q (25, 26), 6q (27), 7q (39, 40), 13q (27, 28), 16q (19, 20, 24, 25, 27), and 18q (18–20). Compared to other studies, however, we observed relatively low frequencies of AI on chromosome 10 (20% overall versus previously reported 62% at 10q22-24; Ref. 37) and 17q (6% versus previously reported 39% and 52%; Refs. 16 and 17). The region on 17q showing the highest rate of AI in the study by Gao et al. (16) included BRCA1. A marker used in our study maps within this region (D17S589) but is centromeric to BRCA1. Of significance in the present report are the novel findings of AI at 21q22.2–q22.3 in 23% of tumors and at 3p25-26 in 20%. In the reports of genome-wide analysis (20, 27, 28), none found AI on chromosome 3 or 21. One of these used Southern blotting (20), and the other two used comparative genomic hybridization (27, 28). Additional fine mapping studies on these chromosomes, however, will be required to verify these findings.

In our study, the marker demonstrating the most frequent AI on 18q was at 18q 21.1, close to the DCC gene. Whereas other studies of AI on chromosome 18 in prostate cancer implicated either DCC (18, 23)
or a region distal to DCC (26), our results suggest that another TSG in the region of, but distinct from, DCC may be important in prostate cancer. A recently identified candidate gene localized to this region is DPC4 (45). It will be important to perform additional high density mapping of this region and to examine DPC4 in more detail to explore its potential involvement in prostate cancer.

Specific chromosomal regions exhibiting AI in the present study are similar to those reported previously for 16q (16q21-24) and 5q (5q21; Refs. 21 and 25). AI was detected with a marker proximal to the Rb gene on chromosome 13; we did not examine Rb itself. Candidate TSGs that map proximal to Rb include BRCA2, DPC1, and DPC2 (46). For chromosome 8, AI was almost always observed at 8p22, a region identified by others (29–31, 35, 36). Imbalance at other 8p loci that have been suggested as regions harboring TSG in prostate cancer (33, 34, 36), or on 8q, was seen in association with 8p22 AI with only two exceptions. Although we did not use markers to identify AI at 8p21 or 8p11, it is striking that 8p22 was invariably involved in this cohort of prostate tumors.

Although our results are largely in agreement with those reported previously, there are some differences. However, because of differences in analytical techniques and populations studied, a comparison of results is difficult. For example, previously reported AI on 8p in prostate cancer ranged from 27 to 65% (21, 29–36). The lower frequencies were found in studies that used paraffin-embedded material (22, 24) or had small numbers of informative tumors (12). With few exceptions, only small numbers of tumors have been examined, and these have been of varied pathological stages, limiting clinical-genetic correlations. Furthermore, the contribution of prostate tumor heterogeneity, which is very likely to exist (47), has rarely been considered. The evaluation of tumor heterogeneity was not a focus of our study, but deserves consideration in future studies. Variations in the state of the tumor tissue (autopsy, frozen, or paraffin-embedded), the number of chromosomes examined, the number of markers used, and the technology employed confound attempts to compare studies. Additional differences among studies include whether visualization or quantitative image analysis were utilized, the criteria established for assessment of imbalance or loss, and differing sensitivities of Southern blotting versus PCR or comparative genomic hybridization studies.

The regions identified as possible sites for TSG relevant to prostate cancer (8p, 6q, 16q, and 18q distal and proximal to DCC) have also been implicated in other cancers. Allelic loss on 8p occurs in hepatocellular carcinoma (48), colorectal carcinoma (31, 48–50), head and neck cancer (51), bladder cancer (52), collecting duct carcinoma of the kidney (53), and non-small cell carcinoma of the lung (54). The regions commonly deleted include 8p23–21.3 (48), 8p12.1–22 (54), and 8p11–12.1 (51). AI on chromosome 16 has been found in breast cancer (55–57) and hepatocellular carcinoma (58–60), and the region implicated were 16q22.1–qter (55–60). Loss telomeric to the DCC gene has been associated with greater than 30% of loci (74). In our study, none of the tumors exhibited this characteristic widespread instability. These data, therefore, suggest that defective mismatch repair, microsatellite instability is usually detected in greater than 30% of loci (74). In our study, none of the tumors exhibited this characteristic widespread instability. These data, therefore, suggest that defective mismatch repair does not play a significant role in sporadic prostate cancer. Additionally, the frequency of instability at any locus (22 of 5803 loci) was extremely low, much lower than that described for other cancers (74).

The prognostic value of AI in prostate cancer is uncertain, possibly because of the small numbers of tumors examined in many studies and the varied clinical and pathological stage of cancers examined. In our study, the cumulative AI on a chromosome or chromosomal arm was not associated with any consistent clinicopathological parameter except for the following: tumors with AI on chromosome 5 or 5q were of higher pathological stage than those without AI; those with AI on chromosomes 10, 16q, and 18q were more likely to be nondiploid; those with AI on 7 and 16q were of older age at diagnosis; and those with AI on chromosomes 8p and 16 were associated with higher Gleason scores. A trend toward higher PSA concentrations was noted in patients whose cancers exhibited AI on chromosome 8, but not 8p specifically. The association of AI at individual loci with these parameters, however, was limited, suggesting that further delineation of AI is required to more fully investigate the role of specific sites as prognostic markers. Although some associations were found in this data set with a variety of clinicopathological parameters, it is important to note that these correlations were sometimes based on small numbers, and multiple statistical tests were performed, inflating the chance of false-positive findings. None of the reported P values are corrected for multiple testing; rather, we caution that these correlations be only tentatively accepted until reproduced independently in other studies.

Although occurring at a consistently high rate, AI on chromosome 8 has been found to be unrelated to the progression of cancer, suggesting that it occurs early in tumorigenesis (30, 36, 38). In our study, chromosome 8 AI was associated with higher Gleason scores but not with any other prognostic parameter. In contrast, Takahashi et al. have suggested that gain of 8p or 8q may be of prognostic relevance in stage T3 prostate cancer (41). The latter study also implicated aneuploidy of chromosome Y in prostate cancer progression. In a small cohort, Brewster et al. (26) found that allelic loss of DCC (or a TSG distal to DCC), APC, and p53 genes was more frequent in advanced rather than localized cancers. At present, however, no molecular marker meets the criteria, established by the American Joint Committee on Cancer, of an important prognostic factor in prostate cancer (75).

In conclusion, we found high rates of AI on multiple chromosomes in prostate adenocarcinoma. These include sites described previously, as well new regions that may harbor TSGs relevant to the process of prostate tumorigenesis. Additionally, it will be important to further characterize known TSGs, such as DPC4 and BRCA2, and determine their role in prostate tumorigenesis. Although the number of patients studied is small, some associations were noted with several clinicopathological parameters. Additional studies, using multiple microsatellite markers clustered at chromosomal regions that frequently exhibit imbalance, are needed to more fully delineate relevant genetic changes in prostate cancer and their correlations with clinicopathological parameters.
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Allelic Imbalance and Microsatellite Instability in Prostatic Adenocarcinoma

Julie M. Cunningham, Ailin Shan, Myra J. Wick, et al.

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