Genetic Analysis of Prostatic Atypical Adenomatous Hyperplasia (Adenosis)

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Atypical adenomatous hyperplasia (AAH) of the prostate, a small glandular proliferation, is a putative precursor lesion to prostate cancer, in particular to the subset of well-differentiated carcinomas that arise in the transition zone, the same region where AAH lesions most often occur. Several morphological characteristics of AAH suggest a relationship to cancer; however, no definitive evidence has been reported. In this study, we analyzed DNA from 25 microdissected AAH lesions for allelic imbalance as compared to matched normal DNA, using one marker each from chromosome arms 1q, 6q, 7q, 10q, 13q, 16q, 17p, 17q, and 18q, and 19 markers from chromosome 8p. We observed 12% allelic imbalance, with loss only within chromosome 8p11–12. These results suggest that genetic alterations in transition zone AAH lesions may be infrequent. This genotypic profile of AAH will allow for comparisons with well-differentiated carcinomas in the transition zone of the prostate. (*Am J Pathol* 1999, 155:967–971)

The transformation of a normal epithelial cell to a cancerous one proceeds from the effects of accumulated mutations in genes controlling cellular differentiation and proliferation. During this progression, cellular intermediates, or precursors, to the cancerous state exist. There are several types of hyperproliferative lesions in the prostate that could represent the cellular intermediate to prostate cancer (PCa). The most common in the prostate and most commonly studied lesions of this type are benign prostatic hyperplasia (BPH, also called nodular hyperplasia), atypical adenomatous hyperplasia (AAH, also called adenosis), and high-grade prostatic intraepithelial neoplasia (HG-PIN). A large body of evidence has associated HG-PIN with moderately to poorly differentiated PCa,¹ whereas BPH is thought to be a benign lesion.² The potential precursor role of AAH, a small glandular proliferation, to PCa is unclear, although it has been suggested that AAH is indeed a premalignant lesion.³

AAH most often occurs in the transition zone of the prostate, a region surrounding the upper portion of the

prostatic urethra, where approximately 24% of prostate cancers arise.^{4–6} Cancers arising in this zone tend to be well-differentiated, with lower Gleason grades and proliferative cell indices.^{6,7} Several characteristics of AAH provide circumstantial evidence relating it to cancer. First, the age at incidence of AAH is lower than that of PCa, and the incidence of AAH increases with age, as does the incidence of PCa.⁵ Second, AAH lesions are often multifocal, as is PCa, and they are found in close proximity to cancer lesions.⁵ In addition, the incidence of AAH increases in the presence of cancer (15% versus 31%),⁵ and, conversely, cancer incidence increases when AAH is present.⁸ AAH also displays several morphological features similar to well-differentiated carcinoma, including a high-density architectural arrangement of small glands, a nuclear and nucleolar volume intermediate between the volume observed in BPH and in carcinoma, a proliferative cell index intermediate between BPH and carcinoma, altered secretory products similar to that seen in PCa, and a fragmented basal cell layer.^{1,5,9} Thus, histologically, AAH appears to exhibit some cancer-like features and for these reasons, it has been suggested that AAH is the precursor lesion to, or an intermediate lesion between BPH and, the subset of well-differentiated cancers arising in the transition zone.^{1,3,10} However, these cellular changes are not exclusive to neoplastic transformation. Fragmentation of the basal cell layer and the presence of nucleoli are occasionally seen in benign lesions.¹¹ Also, the AAH proliferation index is closer to BPH than carcinoma,^{12–14} and AAH cells have a normal (diploid) DNA content.^{13,14} It has been suggested that the association of AAH with carcinoma is merely an epiphenomenon.¹⁵

The identification of genetic alterations is one approach to distinguish benign from potentially cancerous lesions. Regions of frequent chromosomal loss may harbor tumor suppressor genes inactivated during the initiation and/or progression of a particular type of cancer. One study of BPH revealed few genetic alterations, con-

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sistent with a benign classification,² whereas studies of HG-PIN have revealed frequent genetic alterations, such as deletions within chromosomes 8p, 10q, and 16q and gain of chromosome 8q,¹⁶ consistent with a premalignant role. In addition, the presence of HG-PIN has been found to be highly predictive for cancer.^{16,17} AAH lesions have not been studied as intensively as have PIN lesions, most likely because of the difficulty in obtaining samples and sufficient amounts of DNA for analysis. Qian et al¹⁵ previously reported a chromosomal alteration study on AAH lesions using fluorescent *in situ* hybridization (FISH) analysis with centromere probes to chromosomes 7, 8, 10, 12, and Y on 23 AAH foci in 19 whole-mount prostate specimens. They observed only two AAH foci with chromosomal anomalies; one sample demonstrated loss of chromosome 8 only, and the second demonstrated loss of chromosomes 7 and 8.¹⁵ From this study, they concluded that AAH was not an obvious genetic precursor to carcinoma.¹⁵ However, this study was limited by the technique used, which will only detect whole chromosome deletions or large deletions spanning the centromere, and by the small number of chromosomes tested (5 chromosomes). A more recent study by the same group³ reported 47% allelic imbalance (AI) in 15 AAH lesions studied using five polymorphic microsatellite markers on chromosomes 7q (9% AI), 8p (D8S133, 60% AI; D8S254, 18% AI), 8q (15% AI), and 18q (9% AI). They conclude from this study that, although further studies are needed, AAH may represent a genetic precursor to some forms of carcinoma. These AAH lesions were in prostate glands with carcinoma and only 4 chromosomal arms were targeted. The aim of our investigation was to characterize allelic imbalance on 10 chromosomal arms in AAH lesions in patients without prostate cancer. We used allelic imbalance analysis to investigate 25 AAH lesions for regions of chromosomal loss by comparing DNA extracted from microdissected AAH lesions to matched normal DNA, selecting regions of the genome previously suggested to be involved in the development of prostate cancer (chromosome arms 1q, 6q, 7q, 8p, 10q, 13q, 16q, 17p, 17q, and 18q).

Materials and Methods

Surgical Specimens and DNA Extractions

Twenty-four AAH lesions were identified by a review of 752 consecutive transurethral resections diagnosed from 1973 to 1986 as BPH at Barnes Hospital (St. Louis, MO). This was done to identify AAH lesions that were not in a setting of carcinoma. Only one AAH case was identified in a radical prostatectomy specimen which also contained carcinoma. AAH foci were evaluated by a urologic pathologist according to previously defined criteria.¹⁸ Areas of BPH from the same case were used as a source for matched normal DNA. BPH and AAH foci were dissected directly from the paraffin-embedded tissue block, using maps on corresponding H&E-stained slides. DNA extractions were performed as described by Stein and Raoult.¹⁹

Allelic Imbalance Analysis

Twenty-eight polymorphic markers with heterozygosity values of at least 70%, when available were chosen from publicly available databases such as the Genome Database (GDB) or from literature references. A chromosome 8p HRG1 marker (near the Heregulin gene) was developed in our laboratory and will be described elsewhere (Doll JA, Donis-Keller H, manuscript in preparation). Polymerase chain reaction (PCR) reactions contained 10 to 25 ng of template DNA, 1.0–2.5 mmol/L MgCl₂, 2 μmol/L of each primer, 200 μmol/L dNTP mixture, and 0.05 units of *Taq* DNA polymerase (Perkin-Elmer, Norwalk, CT) with one primer end-labeled with [³²P]ATP, using T₄-polynucleotide kinase (New England Biolabs, Beverly, MA) according to the manufacturer's suggestions. Amplifications were performed on Perkin-Elmer 480 or Hybaid Omnigene thermal cyclers. Products were separated on 8% denaturing polyacrylamide gels and vacuum dried. Gels were imaged either by exposure to X-ray film for 12 to 48 hours or to a phosphor storage screen (Eastman Kodak, Rochester, NY). Phosphor storage screens were scanned on a Storm 840 phosphor imaging system (Molecular Dynamics, Sunnyvale, CA). AI was determined either by visual inspection of autoradiographs by three independent researchers or by quantification of the allelic imbalance (AI) ratio on phosphor images, using the ImageQuant v1.1 software (Molecular Dynamics). The criterion for AI was a 50% reduction of an allelic signal of the AAH DNA as compared to the matched normal DNA. The AI ratio was calculated using the following formula: $AI = [Tumor_{large\ allele}/Tumor_{small\ allele}]/[Normal_{large\ allele}/Normal_{small\ allele}]$. AI values greater than or equal to 2.0 (loss of the smaller allele) or less than or equal to 0.5 (loss of the larger allele) correspond to a 50% reduction level. All observations of AI were confirmed by repeating the assay at least twice, and the AI values presented are the average values of the repeated assays.

Results and Discussion

Twenty-four of the 25 cases of AAH were identified out of the 752 transurethral resection cases with BPH, for an incidence of 3.2% AAH in the absence of cancer. No cancer was evident in these 24 cases. The remaining case was identified in a radical prostatectomy specimen containing both BPH and cancer. The AAH foci were characterized by a circumscribed proliferation of densely arranged small acini (Figure 1A). At high magnification, the small glands exhibited minimal luminal cell nuclear atypia with inconspicuous nucleoli and a fragmented basal cell layer (Figure 1B).

DNA from the 25 AAH foci, with matched normal DNA from the same patient, were assayed for AI using microsatellite markers from 10 chromosomal arms. Because AAH lesions are usually small (a few millimeters in diameter), only limited amounts of DNA were available; therefore, loci were chosen based on published reports of frequent sites of AI in PCa or because of a reported association with hereditary PCa. Multiple markers were tested on chromosome arm 8p and one marker was

Table 1. Polymorphic Markers Used in AI Study

Marker (chromosomal localization)	AI observed/ informative samples
D1S2883 (1q24-25)	0/18
D6S262 (6q14-21)	0/19
D7S480 (7q31)	0/19
D8S549 (8p)	0/18
LPL-3' (8p22)	0/22
D8S133 (8p)	0/16
D8S136 (8p)	0/20
SFTP2 (8p)	0/15
NEFL (8p21)	0/13
D8S137 (8p)	0/20
D8S1820 (8p)	0/21
D8S339 (8p12)	0/15
D8S499 (8p)	0/16
HRG1 (8p12)	0/12
D8S283 (8p)	0/24
D8S505 (8p12)	0/17
D8S87 (8p12)	0/16
FGFR1 (8p11-12)	0/17
D8S255 (8p12)	0/18
D8S1104 (8p)	1/21
D8S268 (8p11)	2/21
PLAT (8p12-q11.2)	0/14
D10S541 (10q23-25)	0/18
D13S153 (13q14)	0/20
D16S402 (16q23-24)	0/17
D17S1176 (17p13)	0/13
D17S855 (17q21)	0/23
D18S851 (18q21)	0/21

tested for each of the following chromosome arms: 1q, 6q, 7q, 10q, 13q, 16q, 17p, 17q, and 18q (Table 1). The average number of informative samples per marker was approximately 18, and all DNA samples were informative for multiple loci.

Three of the 25 paired AAH/normal DNAs analyzed (12%) revealed AI at one chromosome 8p locus each. Sample B300 demonstrated AI at the D8S1104 locus, with an average AI value of 2.22, while retaining flanking loci tested. Samples B320 and B324 both demonstrated AI at the D8S268 locus with average AI values of 2.89 and 2.24, respectively. Sample B320 retained the flanking loci; sample B324 was not tested at the flanking loci. Figure 2 shows an example of the data for each of these samples. No AI was observed on other chromosome arms or with other chromosome 8p markers in these samples. Sample B324 was the AAH lesion identified from the radical prostatectomy specimen; however, the cancer lesion (Gleason grade 3+2) did not demonstrate AI with any of the chromosome 8 markers analyzed. Clinical follow-up of the other two patients from which the AAH lesions were obtained was not available.

In the region of deletion in the AAH samples, the marker order is cen-PLAT-D8S268-D8S1104-D8S255-tel, based on the Whitehead Institute for Biomedical Re-

Figure 1. Atypical adenomatous hyperplasia. A: A circumscribed nodule of atypical adenomatous hyperplasia in a transurethral resection of prostate chip. H&E; original magnification, X20. B: High-magnification of small acini of atypical adenomatous hyperplasia. Basal cells are present and nuclear atypia is minimal; these characteristics are essential for a diagnosis of AAH rather than well-differentiated adenocarcinoma. H&E; original magnification, X200.

Figure 2. AAH samples demonstrating AI with markers D8S1104 and D8S268. These are phosphor images as scanned by the Storm 840 phosphor imager. N is the normal tissue DNA lane, and A is the AAH tissue DNA lane. Arrows indicate the lost allele in each of the AAH DNAs. The AI value indicated below each example indicates the value calculated for the assay displayed.

search/MIT Center for Genome Research radiation hybrid (RH) map and confirmed by our own RH mapping efforts (Doll JA, Donis-Keller H, manuscript in preparation). Based on our own RH maps, the D8S1104 and D8S268 loci are separated by approximately 2–4 Mbp (Doll JA, Donis-Keller H, manuscript in preparation). Therefore, the location of the apparent region of deletion lies within an approximately 2–4 Mbp region. Chromosome 8p loss has been consistently reported as the region of highest loss in PCa, with the highest frequency of loss reported in the 8p22 region.^{20,21} In contrast, the three AAH samples demonstrating AI in this study lost markers only in the 8p11–12 region. No loss was observed in the AAH lesions with either of the two chromosome 8p22 markers analyzed, LPL-3' and D8S549. If AAH lesions are indeed the precursor lesion to transition zone cancers, this may indicate that this subset of cancers develops via a different genetic pathway than do peripheral zone cancers. In the study by Qian et al,¹⁵ the authors noted that chromosomal anomalies were more common in peripheral zone cancers than in transition zone cancers (64% *versus* 17%, $P = 0.04$), again suggesting that peripheral and transition zone cancers may be distinctive entities and that genetic alterations occur less frequently in transition zone cancers. Thus, the precursor lesion to this subset of cancers would be expected to have a lower frequency of alterations. However, this is the only study that specifically compares transition zone and peripheral zone cancers. A comparison of well-differentiated cancers (Gleason score [GS] ≤ 4), which occur most often in the transition zone, *versus* moderately to poorly differentiated cancers (GS ≥ 5), which occur most often in the peripheral zone, would be useful; however, few studies include any tumors with GS ≤ 4 , and most studies do not provide sufficient details on the clinical and pathological characteristics of their samples to permit determination of the frequency of genetic alterations in relationship to GS. Comparisons are also difficult due to technical differences between studies. First, the method of detection of genetic alterations differs between studies; those most commonly used are AI, comparative genomic hybridization, and FISH analysis. Second, the chromosomal loci analyzed in each study differ. Third, the stated criteria for loss differ, as do

the initial amounts of cancer cells contained within the samples (ie, the loss criteria range from $<30\%$ to 70% ; and the purity of the samples ranges from 50 to 100%). Also, in some studies, very small numbers of samples are analyzed. Taken together, these differences may explain the high degree of variability between studies in the reported frequencies of chromosomal loss. Because of these limitations, only a rough comparison of lower-grade tumors (GS ≤ 6) *versus* high-grade tumors (GS ≥ 7) is possible based on literature reports for the chromosomal arms analyzed in this study, although for chromosomes 1q, 6q, and 17p there were no available reports comparing the frequencies of deletion between lower-grade and high-grade carcinomas. For chromosomes 7q,^{20,22} 13q,²³ 16q,^{20,24,25} and 17q,²⁶ there appeared to be an increase of deletion in the high-grade tumors, whereas for chromosome 18q²⁰ there appeared to be a decrease. For chromosomes 8p^{20–22,25,27} and 10q,^{20,25,28,29} there are some inconsistencies between reported studies; however, a trend of an increase in frequency of deletion in the high-grade tumors is apparent. Overall, these data suggest that lower-grade tumors may indeed have fewer genetic alterations, a finding consistent with the progression model of tumorigenesis; however, the significance of any of these trends is unclear due to the technical differences between studies. Our review of the literature emphasizes the need for investigators to report the frequency of genetic abnormalities in PCa with precise histological grades (rather than ranges of scores) as well as descriptions of other precise clinical and pathological characteristics of the tumor (clinical stage, pathological stage, tumor size, and zone of origin of the tumor).

In general, PCa is not characterized by large genome-wide genetic alterations.^{20,30} The background or random rate of loss is low. The average fractional allelic loss (number of loci lost in a tumor/number of informative loci) in PCa is $<9\%$, as calculated from the allelotype by Kunumi et al.³⁰ Therefore, in PCa, lower rates of loss are significant, particularly in the transition zone cancers, where fewer chromosomal anomalies have been observed.¹⁵ Alternatively, the well-differentiated transition zone tumors may represent a distinct form of PCa in which the genetic alterations differ from those of peripheral zone cancers; therefore, as yet unidentified regions of the genome, not tested in this study, may be playing a role in this subset of cancers and in the precursor lesion. Another possibility is that AAH lesions are characterized by microdeletions, which would be missed in all types of analyses, including AI analysis, unless the markers or probes used were extremely close to the region of deletion.

The AAH samples used in this study were collected from cancer-free specimens (with the exception of case B324); therefore, they may represent the earliest stage in tumor progression and may contain deletions not detected by this targeted analysis. We observed 12% (3/25) AI in our AAH samples. Our result is similar to the 9% (2/23) value observed by Qian et al¹⁵ using FISH analysis and also similar in that the loss observed was on chromosome 8. However, our AI frequency is much lower than the 47% AI observed in the recent study by Cheng et al.³ There are several possible explanations for the differ-

ences between these studies. First, all of our AAH samples were identified in benign histological settings, whereas in the Cheng et al study,³ all AAH lesions were in prostates removed for carcinoma; therefore, the samples in the latter study may represent a later stage AAH lesion or AAH lesions in prostate glands that were more susceptible to genetic damage and/or experienced greater exposure to DNA-damaging agents. In addition, we used a more stringent AI criterion of 50% reduction of allelic intensity in the AAH sample as compared to the patient matched normal sample, whereas Cheng et al³ used a 30% reduction criterion.

More detailed genetic studies are needed to characterize transition zone cancers and to determine whether or not AAH lesions are the precursor lesion to this subset of cancers. We have examined well-differentiated prostatic adenocarcinomas with Gleason scores of 2 to 4 for allelic imbalance at chromosome 8p (Doll JA, Humphrey PA, Donis-Keller H, manuscript in preparation) and, of interest, detected loss at 8p11–12 in 16% of cases, which is similar to the 12% loss of AAH at 8p11–12. The percentage of well-differentiated carcinomas demonstrating loss over the 8p11–21 region was 30%, which is a higher incidence of loss than AAH. In the future, genotypic characterization of a large number of well-differentiated carcinomas with Gleason score 2–4 specifically of transition zone origin, using markers on multiple chromosomal arms, as in the AAH study presented here, would be desirable. In addition, long-term clinical follow-up data of men with AAH is needed to determine the clinical significance of the presence of this lesion in the prostate. To achieve progress in characterizing and defining the genetic alterations in PCa and its potential precursors, it will be necessary to precisely purify and characterize the population of epithelial proliferations in a given study, which may reveal that different genetic pathways are involved in the initiation and progression of histologically different forms of this malignancy.

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