Comparative allelotyping of the short arm of human chromosome 3 in epithelial tumors of four different types

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Abstract Comparative allelotyping of the short arm of human chromosome 3 (3p) in four types of epithelial carcinomas was performed using an identical set of polymorphic markers. In total, 117 samples of non-papillary renal cell carcinoma (RCC), non-small cell lung carcinoma (NSCLC), carcinoma of uterine cervix (CC), and breast carcinoma (BC) were screened for loss of heterozygosity (LOH) with 10 di-, tri- and tetrameric markers covering nine bands of 3p. High LOH frequencies were detected in at least one locus: RCC (36/43, 84%), BC (20/26, 77%), NSCLC (16/24, 67%), and CC (15/24, 62%). Small interstitial deletions prevailed in BC and CC whereas large continuous and discontinuous deletions were mainly found in RCC and NSCLC. Different epithelial tumors displayed unique LOH profiles with partial overlaps in 3p26.1, 3p21.31, and 3p13. The overlap around D3S2409 (3p21.31) appeared common for RCC, BC and CC.

Key words: Human chromosome 3p; Polymorphic marker; Allele deletion; Loss of heterozygosity profile; Renal cell carcinoma; Lung carcinoma; Carcinoma of uterine cervix; Breast carcinoma

1. Introduction

Allele losses in the short arm of human chromosome 3 (3p) were found to be common in various epithelial tumors including kidney, lung, uterine cervix and mammary gland carcinomas (reviewed in [1]). The crucial role of chromosome 3p was shown directly by detection of tumor suppressor activity in microcell-mediated transfer experiments for regions 3p12–p14 and 3p21–p22, as well as for the VHL gene, located in 3p26.4 (reviewed in [1,2]). Cytogenetic analyses and allelotyping of chromosome 3p in primary, metastatic and benign tumors as well as in preinvasive neoplasia have suggested that 3p deletions are early events in the pathogenesis of various epithelial carcinomas including renal cell carcinoma (RCC) [3], small cell lung carcinoma (SCLC), non-small cell lung carcinoma (NSCLC) [1,4], carcinoma of uterine cervix (CC) [5–8], and breast carcinoma (BC) [9–11]. Until now the VHL gene remains the only candidate gene in 3p for which tumor suppressor function was well documented (see references in [1]).

In order to find new candidate loci for tumor suppressor genes (TSG) a detailed analysis of overlapping deletions was performed for various cancer types: nasopharyngeal carcinoma [12], RCC [2,13–18], CC [19], BC [20,21], lung [22,23] and epithelial ovarian tumors [24]. Overlapping of allele and homozygous deletions was detected not only within one type of malignancy, but also between different types, for example between RCC and SCLC (reviewed in [1]). Homozygous deletions found in region 3p21.31 in the SCLC cell lines NCI-H740, NCI-H1450 and GLC20 [25] and in uncultured tumors [22] were shown to overlap with a homozygous deletion detected in mammary gland cell line HCC1500; these results made it possible to narrow the candidate TSG locus up to 120 kbp [21]. This deletion, as well as homozygous deletion in region 3p12 found for the SCLC U2020 cell line, appeared to overlap with the subchromosomal fragment suppressed tumorigenicity of RCC cell lines which was detected via microcell fusion [18,26]. These results suggest the existence of at least one TSG common for different types of cancer and show that comparative mapping of 3p in various malignancies is important for further identification of candidate TSG.

Earlier [27] chromosome 3p was allelotyped in 40 samples of RCC, endometrial and ovarian tumors applying six tri- and tetrameric markers, and an identical set of markers proved useful for comparative mapping of a certain chromosome in various malignancies. In this study we applied a panel of 10 tetra-, tri- and dinucleotide markers for allelotyping of 3p in 117 samples of RCC, NSCLC, CC, and BC aiming to study the involvement of 3p loci in epithelial carcinomas of different location.

2. Materials and methods

2.1. DNA samples

Forty-three non-papillary (including 33 clear cell) RCC samples, 24 NSCLC (16 squamous cell) samples, 26 BC (16 duct) samples and 24 squamous cell CC samples were used for DNA isolation. Samples of frozen tumor tissues were stored at −70°C. Top and bottom sections (10 μm thick) were stained with hematoxylin and eosin and examined under the microscope. Selected samples containing 60% or more tumor cells, and matched normal tissues were cut

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Abbreviations: BC, breast carcinoma; CHLC, Cooperative Human Linkage Center; CC, carcinoma of uterine cervix; GDB, Genome Data Base; LDB, Location Data Base; LOH, loss of heterozygosity; MI, microsatellite instability; NSCLC, non-small cell lung carcinoma; PAGE, polyacrylamide gel electrophoresis; RCC, renal cell carcinoma; RER, replication error; SCLC, small cell lung carcinoma; TSG, tumor suppressor gene(s); VHL, von Hippel-Lindau disease

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into 20-μm sections for DNA extraction. High-molecular-weight DNA was isolated by the standard procedure with proteinase K treatment at 37°C for 24 h followed by phenol/chloroform extraction and precipitation with ethanol [28]. The DNA preparations were tested by electrophoresis in 1% agarose gel.

2.2. Polymorphic markers, PCR and loss of heterozygosity (LOH) evaluation

Ten markers were chosen from the GDB and CHLC data bases for the nine large cytogenetic bands of 3p on the basis of heterozygosity, location and allele length of polymorphic loci. To avoid CA repeat shadows (see references in [11]), mainly tri- and tetrameric markers (seven loci) were used in combination with non-denaturing 8–12% 20-cm PAGE and silver staining. CA repeat markers were selected to obtain amplification products of size 80–170 bp and sufficient resolution for alleles different in 2 bp. Denaturing 6.5% 40-cm PAGE in combination with ^{32}P-labeled primers and subsequent autoradiography was also applied for ambiguous LOH cases in dinucleotide loci. The order of the selected markers according to the LDB (http://www.cedar.genetics.soton.ac.uk/pub/chrom3/gmap) is: D3S2405 (GGAT2A11)-D3S1286-D3S3047 (GATA85F02)-D3S3527-D3S2420 (ATA25A07)-D3S2409 (ATA10H11)-D3S1766 (GATA6F06)-D3S1481-D3S2454 (GATA52H09)-D3S2406 (GGAT2G03). For tri- and tetrameric markers short CHLC names showing microsatellite motifs are given in parentheses. The location of the markers on 3p is shown in Tables 1–3 and Fig. 2.

The PCR primers were synthesized in the laboratory of Dr. V.P. Veiko (Russian State Genetics Center, Moscow). The PCR reaction mixture (25 ml) consisted of 10 pmol of each primer, 50 ng of template DNA, 1 U of Taq^R DNA polymerase (Biotech, Moscow), 0.2 mM each of dNTP, 67 mM Tris-HCl, pH 8.8, 1.0–2.5 mM $MgCl_2$, 16.7 mM $(NH_4)_2SO_4$ and 0.01% Tween-20. The samples were processed through 30 cycles comprising 1 min denaturation at 94°C, 1 min at the appropriate annealing temperature and 1 min at 72°C, in a Techne PHC-3 thermal cycler. Annealing temperatures and $MgCl_2$ concentrations were used according to the GDB data.

Band intensities for PCR products of high- and low-molecular-weight alleles were compared. The LOH was scored when a ratio of intensities for matched tumor and normal DNAs differed two-fold or more. The LOH data were analyzed by three independent viewers; deviation of LOH profiles was calculated using three sets of observations.

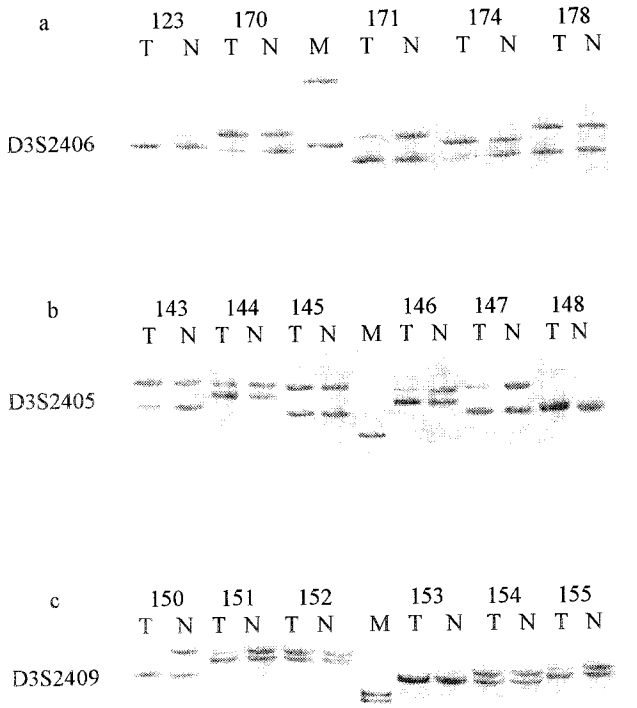

Fig. 1. Examples of tri- and tetranucleotide analysis of tumor DNAs with non-denaturing PAGE followed by silver staining. a: PCR products of some RCC samples in the D3S2406 GGAT repeat locus, separated through 8% PAGE; markers of electrophoresis mobility (M), fragments of pUC19/*Msp*I (404, 331 bp). b: PCR products of some RCC samples in the D3S2405 GGAT repeat locus, separated through 12% PAGE; M, pBR322/*Alu*I (100 bp). c: PCR products of some BC samples in the D3S2409 AAT repeat locus, separated through 12% PAGE; M, pUC19/*Msp*I (111, 110 bp).

3. Results

3.1. Allelotype patterns of 3p in RCC, NSCLC, BC, and CC samples

Fig. 1 shows representative examples of LOH for the RCC and BC samples in tetrameric GGAT and trimeric AAT loci. Application of tri- and tetrameric markers combined with non-denaturing 8–12% PAGE and silver staining allowed us to separate the PCR products with sufficient resolution. The high-molecular-weight allele is lost in RCC samples 171, 146, and 147 and in BC samples 150, 151, and 155 (Fig. 1). The low-molecular-weight allele is lost in RCC samples 170, 174, and 143.

Allelotyping of 3p in NSCLC samples is shown in Table 1. Allelic alterations were revealed in 16 out of 24 samples. More than half of these alterations (10 out of 16 samples) are total losses of one allele of the whole short 3p arm. Sample 179 exhibited a partial terminal deletion. Short interstitial deletions were detected in samples 14 and 55. Multiple discontinuous deletions separated by loci with retained heterozygosity were found in samples 15, 40, and 99. Microsatellite instability

Table 1
Allelotyping of 3p in NSCLC tumors

Marker	Cytogenetic location	Sample No.															
		5	23	38	39	50	60	67	100	130	162	40	15	179	99	14	55
D3S2405	3p26.1	●	●	ni	●	ni	●	●	●	●	●	●	ni	●	ni	○	○
D3S1286	3p25.2	●	●	●	●	●	●	●	●	●	●	○	●	●	●	●	○
D3S3047	3p24.3	●	●	●	●	●	●	ni	●	ni	●	●	ni	●	○	ni	●
D3S3527	3p21.33	ni	●	●	●	●	●	●	●	●	●	●	ni	ni	ni	○	○
D3S2420	3p21.31	●	ni	●	●	●	ni	●	●	●	ni	●	ni	●	●	○	○
D3S2409	3p21.31	●	●	ni	●	●	ni	ni	●	●	ni	●	●	ni	●	○	ni
D3S1766	3p21.1	●	●	●	ni	ni	ni	ni	●	●	●	●	●	○	ni	○	ni
D3S1481	3p14.2	●	MI	●	●	●	●	●	●	●	●	●	○	ni	○	○	○
D3S2454	3p13	ni	●	●	ni	●	●	ni	ni	ni	ni	ni	●	○	ni	○	ni
D3S2406	3p12.2	ni	ni	●	ni	●	ni	ni	ni	ni	●	●	●	ni	ni	○	○

●, loss of heterozygosity; ○, retained heterozygosity; ni, non-informative; MI, microsatellite instability; only cases with detected allelic alteration are shown.

(MI) was detected only in locus D3S1481 in NSCLC sample 23.

Allelic losses in CC samples (Table 2) were revealed in 15 out of 24 samples with frequency similar to NSCLC. However, losses of the whole 3p arm from one chromosome homolog were observed only in four cases (244, 415, 436 and 424) out of 15 and a partial terminal deletion was seen in one sample, 275. Six cases (458, 86, 248, 234, 451 and 418) demonstrated discontinuous multiple deletions of different length and in four other cases (407, 88, 289, and 235) short interstitial deletions were found. Ten MI cases were detected in five CC samples (424, 458, 86, 235 and 459).

Allelotyping of 3p in four epithelial tumors has shown two patterns: one with a considerable contribution of the large continuous and discontinuous deletions for NSCLC (Table 1) and RCC (data not shown) and the other with shorter interstitial and multiple deletions for CC (Table 2) and BC (data not shown).

Allelic alterations of the MI type were observed not as frequently as LOH: one event in one NSCLC sample (Table 1), 10 events in four RCC samples (not shown), 10 events in five CC samples (Table 2) and 16 events in five BC samples (not shown).

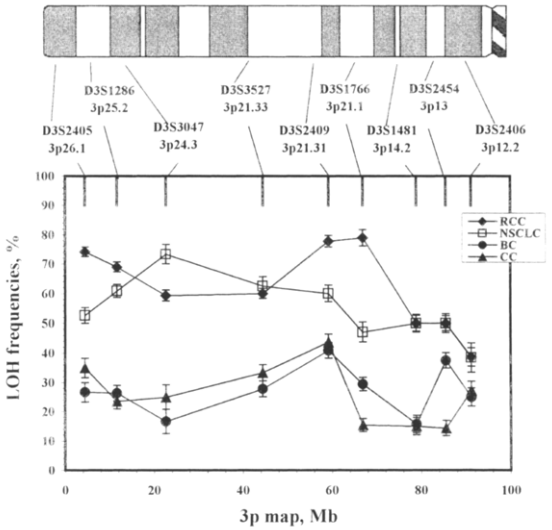

Fig. 2. 3p LOH profiles for RCC, NSCLC, CC, and BC. LOH frequency (Table 3) vs. the map of 3p. Values of LOH frequency for the nine markers related to the nine 3p bands were used. Distances between the markers are shown in accordance with the LDB map. Deviation for three independent viewers is shown.

3.2. Frequencies of allelic alterations

Allelic deletions detected by LOH in at least one locus were highly represented in all studied tumors: RCC (36 samples with LOH from 43 samples studied, 84%), NSCLC (16/24, 67%), BC (20/26, 77%) and CC (15/24, 62%).

The allelotyping data for 43 samples of RCC, 24 samples of NSCLC, 26 samples of BC, and 24 samples of CC were used to calculate the LOH frequencies for the 10 loci of 3p. Each of the polymorphic markers was scored for the number of LOH cases divided by the number of informative cases. The results obtained for four groups of carcinomas are summarized in Table 3. These data demonstrate that average LOH frequencies in the 3p loci are two times higher in RCC (62%) and NSCLC (55%) than in CC (29%) and BC (27%) samples. The higher LOH frequency in the 3p loci in RCC and NSCLC is consistent with the considerable contribution of elongated continuous and discontinuous deletions in these tumors, in contrast to BC and CC with shorter interstitial allele deletions. Therefore, according to the type and the size of deletions epithelial carcinomas may be divided into two groups: with large deletions and high frequency of LOH in the 3p loci (RCC and NSCLC) and with short interstitial deletions and a two-fold lower frequency of LOH in the 3p loci (CC and BC).

DNAs with MI in one or more loci comprise from 4% (1/24) for NSCLC, 12% (5/43) for RCC, 15% (4/26) for BC up to 20.8% (5/24) for CC. This is considerably less than the frequency of cases with LOH (62-84%). Replication error (RER) phenotypes (see references in [1]), detected by two or more MI events found for 10 loci, were observed with a frequency of 7–8% in RCC (3/43), BC (2/26) and CC (2/24). Interestingly, most samples with single MI and all samples with an RER phenotype exhibited LOH. Presumably, there is a positive rather than negative correlation between LOH and MI events on 3p.

3.3. 3p LOH profiles for various carcinomas

The LOH frequencies taken from Table 3 are presented in Fig. 2. The much higher location of the RCC and NSCLC profiles clearly demonstrates higher LOH frequencies in these tumor types for each of the markers. In the RCC and NSCLC profiles telomeric peaks (75%) are higher than in centromeric loci (50%). High LOH frequencies in telomeric loci are related to the contribution of terminal deletions of different size and

Table 2
Allelotyping of 3p in cervical tumors

Marker	Cytogenetic location	Sample No.															
		244	415	436	424	458	86	248	234	418	275	451	235	289	88	407	459
D3S2405	3p26.1	●	ni	●	●	ni	ni	●	●	○	●	●	○	○	○	ni	ni
D3S1286	3p25.2	ni	●	ni	●	●	MI	○	○	○	ni	○	ni	○	●	○	MI
D3S3047	3p24.3	ni	●	ni	MI	MI	●	○	ni	●	ni	ni	ni	○	○	ni	ni
D3S3527	3p21.33	●	●	●	MI	○	●	●	ni	○	●	○	○	○	○	○	○
D3S2420	3p21.31	●	●	●	●	●	ni	●	●	○	○	○	MI	○	ni	●	ni
D3S2409	3p21.31	●	●	ni	●	●	MI	○	○	●	○	ni	●	●	○	○	ni
D3S1766	3p21.1	ni	●	ni	ni	ni	ni	●	○	ni	○	ni	○	○	○	○	○
D3S1481	3p14.2	ni	●	●	MI	ni	○	○	○	○	○	●	○	○	○	○	○
D3S2454	3p13	ni	ni	●	MI	ni	ni	ni	ni	ni	○	ni	○	ni	ni	○	ni
D3S2406	3p12.2	●	●	●	MI	●	●	○	○	○	ni	●	○	○	○	○	○

●, loss of heterozygosity; ○, retained heterozygosity; ni, non-informative; MI, microsatellite instability; only cases with detected allelic alteration are shown.

Table 3
Frequencies of LOH in 3p loci in four tumor types

Marker	Cytogenetic location	RCC	NSCLC	BC	CC
D3S2405	3p26.1	23/31, 74%	10/19, 52%	4/15, 27%	7/20, 35%
D3S1286	3p25.2	20/29, 69%	14/23, 60%	5/19, 26%	4/17, 24%
D3S3047	3p24.3	16/27, 59%	11/15, 73%	2/12, 17%	3/12, 25%
D3S3527	3p21.33	18/30, 60%	10/16, 62%	5/18, 28%	6/18, 33%
D3S2420	3p21.31	17/25, 68%	10/18, 55%	4/19, 21%	8/19, 42%
D3S2409	3p21.31	14/18, 78%	9/15, 60%	9/22, 41%	7/16, 44%
D3S1766	3p21.1	15/19, 79%	8/17, 47%	5/17, 29%	2/13, 15%
D3S1481	3p14.2	8/16, 50%	10/20, 50%	3/19, 16%	3/20, 15%
D3S2454	3p13	8/16, 50%	5/10, 50%	6/16, 38%	1/7, 14%
D3S2406	3p12.2	12/31, 39%	5/13, 38%	5/20, 25%	6/22, 27%
Average		151/242, 62%	92/166, 55%	48/177, 27%	47/164, 29%

The number of LOH cases/informative cases, % are shown.

possible involvement of VHL or other candidate TSG in tumorigenesis.

The 3p LOH profiles for different epithelial tumors appeared to be distinguishable (Fig. 2). The NSCLC profile showed a major peak in 3p24.3 (D3S3047) and additional regions of high LOH around D3S2409 (3p21.31) and D3S2454 (3p13). The RCC profile possessed a major peak encompassing two cytogenetic bands, 3p21.31(D3S2409) and 3p21.1 (D3S1766), and high deletion frequencies in 3p26.1 (D3S2405) and in 3p13 (D3S2454). The BC LOH profile included regions of high LOH around D3S2409 (3p21.31) and D3S2454 (3p13). The CC profile had a region of high LOH around D3S2409 (3p21.31) and D3S2405 (3p26.1).

Partial overlaps may be seen in certain 3p regions. Overlap around D3S2409 (3p21.31) seems to be common for at least three malignant neoplasias: RCC, CC and BC (Fig. 2). Additional overlaps were found in telomeric region 3p26.1 (D3S2405) for RCC and CC, and in 3p13 (D3S2454) for RCC, NSCLC, and BC. The loci D3S1766 in 3p21.1 and D3S3047 in 3p24.3 were typical for RCC and NSCLC, respectively.

4. Discussion

The problem of involvement of different chromosomes in the development of certain cancer types was studied using comparative cytogenetic and LOH approaches for RCC [29,30], adenocarcinoma and squamous cell carcinoma of the lung [3,31], invasive CC [32–34], and BC [11]. An extensive karyotyping of 3185 tumors [35] included both analysis of the contribution of various chromosomes in a certain type of malignancy and the detection of damage of a certain chromosome for various types of cancer. These data may serve as a guide for more detailed molecular studies. However, no comparative allelotyping analyses were performed until now for a certain chromosome and various types of malignancies.

Mapping of human chromosome 3p using the LOH strategy was performed for epithelial tumors of various locations by several research groups. The results on the character of deletions and on the regions most affected by deletions are often rather controversial even within one form of malignancy, for example RCC [14–16]. This diversity may be explained by different procedures used for evaluation of LOH and for selection of material (short-term cell lines were used only by one group [14]) and by different sets of markers. For example, 2–3 different markers were applied for telomeric region 3p26–p25 in each of the three above-mentioned studies [14–16]; only one marker (D3S1560) was coincident in the two studies.

This work presents the first comparative allelotyping study of human chromosome 3p in different malignancies with identical set of the markers and identical procedures for selection of material and processing of the LOH data. These comparisons have revealed critical 3p regions for each form of the malignancy and regions of their overlapping.

Common features may be seen in the cytogenetic profiles of 3p deletions [35] and in the LOH profiles obtained in this work. For example, in both cases (compare Fig. 2 and the chromosome 3 profile from [35]) the main peak for RCC is more centromeric than the critical region for lung carcinoma.

Our results are consistent with the earlier data on 3p allelotyping obtained for certain types of tumors. For example, the frequencies of allelic deletions detected by the LOH analysis in at least one 3p locus were 62% and 77% for CC and BC, respectively; this is close to the data for CC (70% [19]) and BC (52% [20]). The LOH frequency for various markers varied from 15 to 45% [20] and from 16 to 41% in this work; 26% and 29%, respectively, for the common D3S1286 marker. Our results are in good agreement with the data [13,15,16], showing a considerable contribution of discontinuous multiple deletions in the development of RCC.

The frequencies of MI events (12–21%) and RER phenotype (7–8%) found here for RCC, BC and CC are consistent with earlier observations [11,15,34]. The low incidence of MI in NSCLC has already been mentioned [22]. The positive correlation between LOH and RER shown here for the 3p region may be related to the deletion of the MLH1 repair system gene located in 3p22–p21.33 (see references in [1]).

New candidate loci for genes associated with cancer were found in several regions of 3p. The locus localized around D3S2409 (3p21.31) seems to be common for at least three epithelial carcinomas. According to the LDB map the new candidate locus is centromeric to both known homozygous deletion regions found earlier in 3p21.3 [22,25,36–38].

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