American Journal of Pathology, Vol. 156, No. 3, March 2000

DNA Copy Number Changes in *Schistosoma*-Associated and Non-*Schistosoma*-Associated Bladder Cancer

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DNA copy number changes were investigated in 69 samples of schistosoma-associated (SA) and non-schistosoma-associated (NSA) squamous cell carcinoma (SCC) and transitional cell carcinoma (TCC) of the bladder by comparative genomic hybridization (CGH). DNA copy number changes were detected in 47 tumors. SA tumors had more changes than NSA tumors (mean, 7 *vs.* 4), whereas the number of changes in SCC and TCC tumors was similar. SA tumors displayed more gains than losses (1.7:1), whereas NSA tumors showed an equal number of gains and losses. Changes that were observed at similar frequencies in SCC and TCC, irrespective of the schistosomal status, included gains and high-level amplifications at 1q, 8q, and 20q and losses in 9p and 13q. These changes may be involved in a common pathway for bladder tumor development and progression independent of schistosomal status or histological subtype. Losses in 3p and gains at 5p were seen only in SCC ($P < 0.01$) and losses in 5q were more frequent in SA-SCC than in other tumors ($P < 0.05$). However, changes that were more frequent in TCC than those in SCC included gains at 17q ($P < 0.01$) and losses in 4q ($P < 0.05$) and 6q ($P < 0.01$). Gains and high-level amplifications at 5p were seen only in SA-SCC ($P < 0.01$), whereas gains and high-level amplifications with minimal common overlapping regions at 11q13 were more frequently seen both in SA-SCC and SA-TCC tumors ($P < 0.01$). In addition to the above mentioned alterations, several other changes were also seen at lower frequencies. The variations in the DNA copy number changes observed in TCC, SCC, SA, and NSA bladder carcinomas suggest that these tumors have different genetic pathways. *(Am J Pathol 2000, 156:871–878)*

In Western countries, more than 90% of primary bladder carcinomas (BC) are transitional cell carcinoma (TCC), whereas squamous cell carcinoma (SCC) comprises less than 10%.[1] Carcinoma of the urinary bladder is the most common malignancy in many tropical and subtropical countries due to endemic infection by *Schistosoma hematobium. Schistosoma*-associated bladder carcinoma (SA-BC) defines a characteristic pathology that differs from non-*schistosoma*-associated bladder carcinoma (NSA-BC).[2]

Bladder cancer complicating schistosomiasis constitutes 30.8% of all cancers in Egypt, ranking first among the reported malignancies in Egyptians.[3] Egypt has the highest frequency of bladder cancer in the world. In contrast to Western countries, more than two-thirds of bladder cancer in Egypt are SCC with a peak incidence at around 50 years of age.

The chromosomal alterations in Western TCC have been extensively studied. About 140 tumors have been studied by banding cytogenetics[1,4] and 212 tumors by comparative genomic hybridization (CGH).[5–10] These studies have shown several numerical and structural chromosomal aberrations involving mainly chromosomes 3, 5, 7, 8, 9, 17, and 20. In contrast, only four cases of SCC have been analyzed cytogenetically[11–13] and there are no cytogenetic reports on SA-BC.

Supported in part by grants from the Finnish Cancer Society and the Helsinki University Central Hospital (grants TYH0049 and -8219) in Finland, the schistosomiasis research project (nos. 03-11-35 and 07-01-63) in Egypt, the National Agency of Scientific and Technological Promotion (Contract grant: BID 802/OC-AR PICT No. 01-00000-00753) in Argentina, and the Gillson Scholarship (to M. S.) from the Worshipful Society of Apothecaries of London, UK.

Accepted for publication November 4, 1999.

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The most common genetic alteration identified in TCC is loss of heterozygosity (LOH) on 9p21, where the tumor suppressor gene *p16* is located.[14–16] Mutations and nuclear accumulation of p53 are frequently seen in NSA-TCC[17,18] and were demonstrated in SA-SCC.[19,20] However, the proportion of *TP53* mutations of basepair substitution at CpG dinucleotides was significantly higher in SA-BC than in NSA-BC.[21]

The cytogenetic data available from some studies on Western NSA-TCC have been obtained using fluorescent *in situ* hybridization on SA-BC with probes for chromosomes 7, 9, and 17.[22,23] Although these studies have shown differences between frequencies of chromosomal changes in invasive SA-SCC and SA-TCC or NSA-TCC, they do not provide an overview of the chromosomal alterations in SA-BC.

CGH enables the screening of entire tumor genomes for gains and losses of DNA copy number and consequent mapping of aberrations to chromosomal subregions.[24,25] So far, only NSA-TCC has been studied by this technique. In this study, we used CGH to compare the DNA copy number changes in SA-TCC, NSA-TCC, and SCC of the bladder.

Materials and Methods

Characterization of Tumors

A total of 69 cases of primary bladder carcinomas were obtained. Thirty-eight cases were SA-BC and 31 NSA-BC. All SA-BC and 16 of the NSA-BC were collected from the files of the Pathology Department, National Cancer Institute (Cairo, Egypt) and 14 cases of the NSA-BC were collected from the files of The Institute of Pathology, The Royal London Hospital (London, UK). All of the material consisted either of cystectomy specimens or surgical biopsies and was obtained either as frozen tissue sections (41 samples) or fixed in 10% buffered formalin and paraffin-embedded (28 samples) as shown in Table 1. The diagnosis, classification, and tumor grading were based on light microscopy examination using the criteria of the World Health Organization (WHO) classification of urinary bladder carcinomas.[26] Of the 38 SA-BC, 28 were SCC and 10 were TCC, and of the 31 NSA-BC, 18 were SCC and 13 were TCC. The SCCs had squamous cell differentiation in the entire tumor. SA-BC was histologically verified by the presence of schistosomal cystitis in the bladder mucosa close to the tumor. The stages of paraffin-embedded tumors were comparable to those of frozen tumors. Sixty-three tumors (91%) were staged as pT2-pT4, one tumor as pT1, and five tumors as noninvasive pTa (NSA-TCC; Table 1).

CGH

DNA was extracted from frozen tissue sections following standard methods, whereas DNA from paraffin-embedded tissue sections was extracted as described earlier.[27]

CGH was performed according to standard procedures[28] with a modification using a mixture of fluorochromes conjugated to dCTP and dUTP nucleotides for nick translation.[29] Hybridizations, washings, and ISIS digital image analysis (Metasystems GmbH, Altlussheim, Germany) were performed as described elsewhere.[30] Three-color images (red for reference DNA, green for tumor DNA, and blue for counterstaining) were acquired from 8 to 10 metaphases per sample. Only metaphases of good quality with strong uniform hybridization were included in the analysis. Chromosomes not suitable for CGH analysis (ie, chromosomes heavily bent, overlapping, or with overlying artifacts) were excluded. Based on our earlier reports and the control results, we used 1.17 and 0.85 as cut-off levels for gains and losses, respectively.

Controls

In each CGH experiment, a negative control (peripheral blood DNA from a healthy donor) and a positive control were included. The positive control was a gastric tumor with known DNA copy number changes.

Statistical Analysis

All of the CGH results were confirmed using a 99% confidence interval. Briefly, intraexperiment standard deviations for all positions in the CGH ratio profiles were calculated from the variation of the ratio values of all homologous chromosomes within the experiment. Confidence intervals for the ratio profiles were then computed by combining them with an empirical interexperiment SD and by estimating error probabilities based on the *t* distribution. For the analysis of the frequencies of DNA copy number changes in BC histological subtypes, we used Fisher's exact two-tailed test. P values <0.05 were considered significant.

Results

Changes in DNA copy numbers were detected in 47 tumors, 26 SA-BC, and 21 NSA-BC. A total of 149 gains and 96 losses was detected. Tumors that had no CGH changes included 6 SA-SCC, 7 NSA-SCC, 6 SA-TCC, and 3 NSA-TCC. SA-BC had more changes than NSA-BC (mean, 7 and 4, respectively), whereas SCC and TCC showed a comparable number of changes. SA-BC displayed more gains than losses (1.7:1), whereas NSA-BC had an equal number of gains and losses. No differences were noticed in the CGH results between DNA extracted from frozen and paraffin-embedded tissue sections.

Because CGH sensitivity requires at least 50% of tumor material within a sample, tumors without alterations (Table 1) were excluded from the interpretation of the results and from the statistical analysis as they may reflect a high contamination by normal cells within the tumor material. In addition, four pTa tumors that had CGH changes (Table 1) were excluded from the statistical analysis as they may represent an entirely different tumor entity from invasive bladder carcinomas. Among the ab-

Table 1. Histopathology and CGH Karyotype in Squamous and Transitional Cell Bladder Carcinomas

No./age/sex/ sample codes	Pathology			CGH karyotype	
	Tissue	Grade	Stage	Losses	Gains
Schistosoma-associated SCC					
1/26/F B11	PF	I	T3	2q31-q33, 3p12-q13, 4q, 8p, 9p21-pter	2p22-pter, 4p, 6p, 8q, 9q, 11q13, 15q22-qter, 20q12-qter
2/35/M B03	PF	II	T3	3p, 4q11-q28	5p15, 8q, 11q13-q22
3/60/M B05	PF	II	T3	4q24-qter, 13q21-q22	5p
4/42/M B14	PF	II	T3	4, 5q, 13q21-q31	1q24-qter, 7q
5/38/M B16	PF	II	T3	3p14-q13, 4, 5q15-q23, 9p	2p22-pter, 2q14-q21, 8q24, 11q11-q21, 15q14-qter
6/52/M B25	PF	II	T3	8p, 13q21-q31	1q21-q24, 4p, 8q
7/74/M B32	PF	II	T3	5q11-q22, 6q, 9p21-pter, 13q21.2-q31, 14	1q21-q24, 2q12-q21, 3p21-pter, 5p, 7q33-qter, 8q22, 11q11-q13, 12q (**12q14-q15**), 17q, 20q12-qter
8/45/M B37	PF	II	T3	4q, 13q21.1-q22	6p, 7
9/51/M B53	PF	II	T3	13q13-qter	11q11-q13
10/35/M B24	PF	II	T3	–	11q13
11/55/M BC-22 89-1412A	FZ	II	T3	5q	17q
12/49/F BC-49 89-1294A	FZ	II	T3	5q11-q31	8q22-qter, 11q11-q13
13/60/M BC-16 89-1294A	FZ	II	T3	–	5p14-pter, 11q13-q14.2
14/53/M BC-6 89-1394A	FZ	II	T3	–	1q21-q24
15/35/M BC-33 89-1822A	FZ	II	T3	3p, 11q22-qter	11q13
16/54/M B29	FZ	III	T3	13q21-q31	11q11-q13
17/65/M B56	PF	III	T3	3p, 4, 5q, Xp, 8, 9, 10q22.2-qter, 11p13-pter, 13q13-q32	**5p**, Xq, 10pter-q22.1, 11q11-q14, 12, 17q, 19, 20 (**20q**), 22
18/41/M B21	PF	III	T3	9p21-pter	5p, 6p, 8p12-qter, 11q13, 11q22-q23.2, 20q12-q13.2
19/51/M BC-50 89-1821A	FZ	I	T4	3p, 13, 18q	3q, 6p22-pter, 8q21-qter, 17q
20/39/M B13	PF	II	T4	18	4p15, 6p, 8q (**8q24**), 11q13, 14q21-qter, 15, 17q, 20q, 22
21/55/M B34	PF	II	T4	13q13-q31, 9p21-pter	1q21-q25, 6p, 8p21-pter, 9q34, 12q13-q21 (**12q14-q15**), 17q, 20q
22/50/M B52	PF	III	T4	5q14-q23, 6q, 13q21-q31	5p, 7pter-q21, 9, 11q, 20
Non-*Schistosoma*-Associated SCC					
23/56/M BC-5 SD 71/94	FZ	I	T2	13q	–
24/53/M B20	PF	I	T3	–	8q (**8q24**)
25/48/M B38	PF	II	T3	6q11-q15, 13q21-q31	–
26/77/F BC-11 SD-2004/94	FZ	II	T3	13q13-q31, 18q12.2-q22.2	–
27/45/M B26	PF	III	T3	–	1q, 8q22-qter, 9q22-qter, 20q12-qter

FZ, frozen tissue; PF, formalin-fixed paraffin-embedded tissue; Ta, papillary, non-invasive; T1, invasion limited to lamina propria; T2, invasion limited to inner half of muscularis propria; T3, invasion into outer half of muscularis propria or the perivesical fat; T4, invasion to contiguous viscera or pelvic organs; SCC, squamous cell carcinoma; TCC, transitional cell carcinoma.

High-level amplifications are in bold type.

Table 1. Continued

No./age/sex/ sample codes	Pathology			CGH karyotype	
	Tissue	Grade	Stage	Losses	Gains
28/42/F B02	PF	III	T3	–	20q12-qter
29/61/F B01	PF	II	T4	–	8, 17
30/70/M B19	PF	II	T4	2q31-q35	3q, 4p16, 6p22-pter, 8q23-qter (**8q24**)
31/72/F BC-39 SD 5833/93	FZ	II	T4	4q21-qter, 6q14-q22, 13q14.2-q31.2	1q21-q23
32/85/F BC-13 SD 4773/88	FZ	III	T4	3p, 4, 5q, 9p21-pter, 10p, 18q	1q, 2p, 3q, 7q, 11q11-q21(**11q13**), 17q11-q22, 18p, 20q, 22
33/78/F BC-48 SD 2031/88	FZ	III	T4	3p13-q13, 13q21-q32	11q13, 20q
Schistosoma-Associated TCC					
34/63/M B28	PF	III	T3	4, 6q11-q22, 8q11-q13, 10q11-q21, T1p, 13q11-q32, 18q21-qter	3p21-pter, 3q, 7, 8q21.3-qter, 9p, 11q11-q14, 11q23-qter, 12q23-qter, 20
35/60/M BC-43 89-1660A	FZ	III	T3	–	7q, 11q13-qter, 17q, 20q
36/46/M BC-41 89-1854A	FZ	III	T3	4, 9p	3p14-pter, 8q22-qter, 17q, 20q
37/66/M BC-21 89-1315A	FZ	III	T4	4p	1q21-q31.2, 10p, 11q11-q13
Non-*Schistosoma*-Associated TCC					
38/90/M BC-31 SD 4194/94	FZ	II	Ta	2q23-qter, 4q22-qter, 11p13-pter, 13	1q21-q31 (**1q22-q23**), 4p15-pter, 6p, 10p, 18p
39/70/M BC-15 SD 637/94	FZ	II	Ta	8p, 9p21-pter, 11q22.2-qter, 18q	–
40/77/F BC-32 SD 4535/94	FZ	II	Ta	2q23-q32,4, 13q21-qter	1q22-q24, 11q13
41/76/F BC-17 SD 3401/94	FZ	II	Ta	18q	17q, 20q (**20q13.1**)
42/78/M BC-30 SD 3158/94	FZ	II	T1	4q13-qter, 9p21-pter, 13q21-q31	1q21-q25, 15, 19, 20 (**20q13.1-qter**), 22
43/64/F B18	PF	II	T3	2q24-q33	2p22-pter, 6p, 8q23-qter, 17q
44/53/M B04	PF	III	T3	6q11-q23	11q13
45/81/F BC-29 SD 5877/94	FZ	III	T3	6q13-q21, 13q21-q31	17q, 20
46/46/M B27	PF	II	T4	6q11-q21	7p13-p21, 8q24, 11q13-qter
47/83/F BC-47 SD 3766/94	FZ	III	T4	4q23-qter, 6q16-q23,, 9p, 13q13-q22	1q22-q24, 8q23-qter, 17q

normal cases, the common overlapping regions of the most frequent changes were defined as follows. Gains and high-level amplifications at 11q13 were seen in 65% of SA tumors compared to 23% of NSA tumors ($P < 0.01$). Gains and high-level amplifications at 5p (21%) and losses in 3p (24%) were only seen in SCC tumors ($P < 0.01$). The gains at 5p were limited to SA-SCC (32%, 7 tumors, $P < 0.01$) and losses in 5q were more frequent in SA-SCC ($P < 0.05$). Changes that were more frequent in TCC than SCC tumors included gains at 17q11-q22 (50% *vs.* 24%, $P < 0.01$) and losses in 4q24-qter (40% *vs.* 27%, $P < 0.05$) and 6q11-q21 (50% *vs.* 12%, $P < 0.01$). Gains and high level-amplifications at 1q, 8q24, and 20q12-q13, and losses in 9p and 13q21-qter were seen equally in both SCC and TCC irrespective of the schistosomal status. Other changes were seen as gains at 1q, 2p, 3q, 7, 9, 12q, 14, 15, and 22, and losses in 2q, 3p, 5q, and 18q.

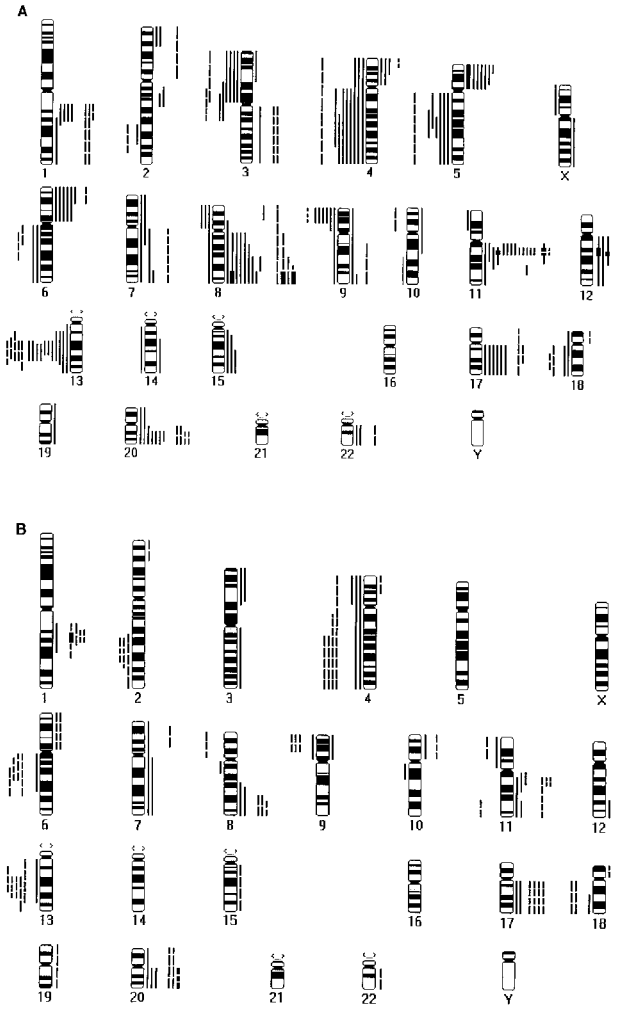

Figure 1. Summary of DNA copy number gains and losses detected by CGH in bladder cancer. **A:** Squamous cell carcinoma. **B:** Transitional cell carcinoma. Each bar represents one tumor sample. Gains are on the right hand side, losses on the left. Continuous lines represent schistosoma-associated tumors, broken lines non-schistosoma-associated tumors, and bold lines high-level amplifications.

The details of DNA copy number changes are shown in Table 1 and Figure 1. Figure 2 shows the relative frequencies of the aberrations among abnormal cases.

Discussion

We undertook to compare, for the first time, the DNA copy number changes in SCC and TCC in both SA and NSA tumors. Although most of the tumors were high-grade/high-stage, our results indicate that some of the recurrent changes were common for all BC subtypes, whereas others were more frequent in a certain histological subtype.

SA-BC versus *NSA-BC*

The higher number of copy number changes observed in SA-BC than in NSA-BC may be explained by the chromosome instability mediated by either reactive oxygen species or urinary nitrosamines as a result of chronic inflammation and irritation in the urinary bladder by schistosomal infection.[31] Schistosomal infection has been reported to be directly involved in increased chromosomal breakage in the urothelial cells at the micronuclei level.[32]

Gains and high-level amplifications at 11q13 were significantly higher in SA-BC than in NSA-BC, indicating that 11q13 gains may be related to the schistosomal status irrespective of the histological subtype. Possible involvement of loci in chromosome 11 in controlling the level of chromosomal breakage caused by oxidative damage due to chronic schistosomal infection has been suggested earlier.[31] Among all reports of CGH studies on TCC, 11q13 gains have been rare (28 tumors, 15%) and the rate is thus comparable to NSA-BC in our material. In one study, 11q13 gains were more frequently seen in pT1 tumors than in pTa tumors.[10] However, all other CGH studies[5–9] have shown this gain to be rare and not associated with tumor stage.

Gains and high-level amplifications at 5p were seen only in SA-SCC. This gain has been less frequently reported (17%, 32 tumors) in CGH studies of TCC[5–10] and has been detected mainly in advanced TCC (pT2 and higher).[9] Cytogenetic data on TCC have shown isochromosome 5p to be the underlying mechanism of 5p gain.[1] One of our cases (no. 17) had a high level-amplification at 5p with a loss of whole 5q, which is likely to be an isochromosome 5p.

Changes involving other chromosomal regions were almost equally distributed among SA-BC and NSA-BC indicating that they may be related to bladder tumors rather than to schistosomal status.

SCC versus *TCC*

In the present study, gains and high-level amplifications at 5p and losses in 3p were seen only in SCC tumors. Although gains at 5p were exclusively seen in SA-SCC, a similar finding has been reported in advanced TCC.[6] Because secondary SCC can in rare instances develop on top of advanced TCC, gains at 5p may be one of the changes required for SCC differentiation. Alternatively, the high frequency of 5p in SCC may be explained by the higher stage of SCC compared to TCC. Earlier CGH studies have indicated that 3p losses are rare among the abnormal TCC (9 of 186, 5%).[5–9] Losses in 3p had a minimal common overlapping region at 3p12, which coincides with loss of heterozygosity studies that showed that deletions at 3p12 are rare and occur only in invasive TCC tumors.[33] Losses in 5q have rarely been reported in earlier CGH studies and were more frequent in our SA-SCC, indicating that the role of this change is more significant in the development of SA-SCC than in other histological subtypes.

Our results showed that some changes were more frequent in TCC than in SCC, such as gains at 1q21-q24 and 17q11-q22 and losses in 4q24-qter and 6q11-q21. Earlier CGH studies and molecular studies have indicated that these changes are more frequent in advanced TCC.[6,10,34,35] A fluorescence *in situ* hybridization study

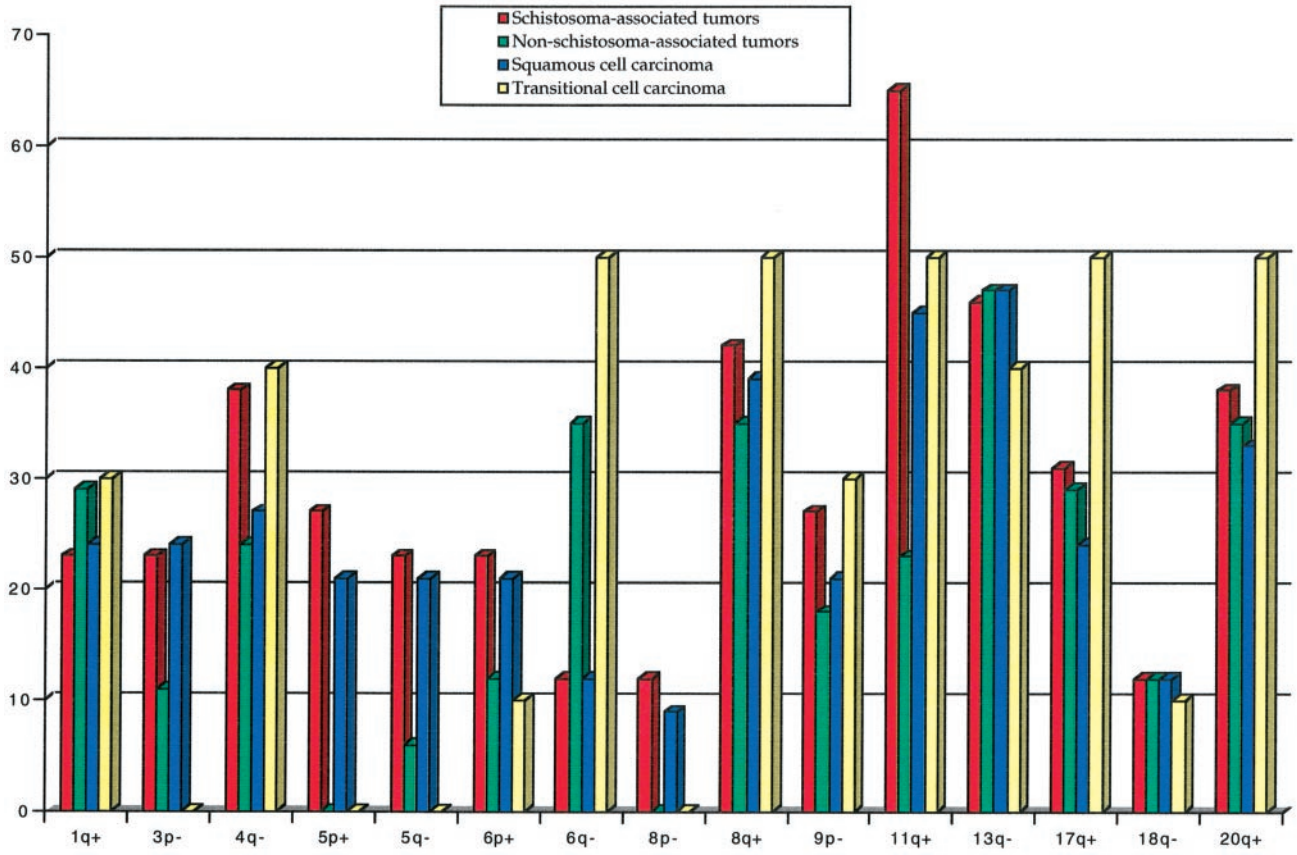

Figure 2. Comparative frequencies of common losses (−) and gains (+) detected in bladder tumors. Tumors with normal CGH and pTa tumors are excluded.

has shown that the number of gains at chromosome 17 was significantly higher in TCC than in SCC,[23] which is in agreement with our finding. Other changes have not been investigated in SCC. Almost all our tumors (88%) were histologically above pT2. Therefore, these changes seem to be more related to tumor progression in TCC than in SCC.

Frequent changes that were equally seen in SCC and TCC included gains and high level amplifications at 8q24, 11q13, and 20q12-q13 and losses in 9p and 13q21-qter. Gains at 8q and 20q have been reported in advanced TCC[6,10] and in several malignancies such as breast, colon, and stomach cancer.[25] The five pTa tumors in our material showed no gains at 8q and the frequency of 20q gains was low. Because most of our tumors were histologically advanced, our data together with earlier CGH and cytogenetic reports on TCC suggest that the aforementioned genetic changes are related to advanced invasive bladder tumors and are independent of the schistosomal status or the histological subtype. However, losses in 9p have been reported in both early TCC and advanced TCC on CGH[5–10] and cytogenetic studies.[1] Although chromosomal deletion at 9p was reported to be more frequent in SCC than in TCC,[23] we did not notice a similar trend, which suggests that losses in 9p are equally important for the pathogenesis of both TCC and SCC. However, losses in chromosome arm 9q, which were commonly seen in Western TCC, were rare in our material. This discordance may be attributable to differences in epigenetic and environmental factors in Western and Egyptian cases. A similar observation was made in gastric cancer (GC). Gains and high-level amplifications at chromosome arms 17q and 20q, characteristic of Western GC,[36,37] were rarely seen in Japanese GC.[38] Egypt has the highest frequency of bladder cancer and Japan, similarly, has the highest frequency of GC.

In addition to the gains at 11q13, losses in 13q were the most frequent change observed in our tumors. Losses in 13q occurred equally among SA-BC and NSA-BC. 13q losses have rarely been reported in earlier CGH studies (10%, 18 tumors)[5–10] of pTa to pT2 tumors. CGH studies on SCC of the head and neck[39–41] have shown a pattern of genetic alterations similar to that observed in our bladder SCC, such as frequent gains at 5p and 11q13. Despite the similarities, gains at 3q and 9q, which were among the most frequent changes seen in SCC of the head and neck,[39,41] were rarely seen in our bladder tumors, and losses in 4q and 13q that were common in SCC of the bladder, mainly SA, were rarely observed in SCC of the head and neck. This suggests that the oncogenesis of SCC may require certain genetic alterations, whereas additional tissue-specific alterations are needed for the tumor development.

DNA Copy Number Changes and Genes

Most of the changes observed in bladder tumors have also been reported in other tumors and some of these

regions are known to contain oncogenes and tumor suppressor genes.[25] Although 11q13 gains are rare in TCC, DNA amplification of four proto-oncogenes, *cyclin D1, FGF3, FGF4,* and *EMS1*, was found in 11% of TCC (5 of 46 tumors).[42] Gains and high-level amplification at 1q21-q24, 8q24, 17q11-q22, and 20q were reported in several tumors such as breast, colon, and stomach cancer, and in osteosarcoma.[25] 1q21-q24 contains oncogenes such as *SKI*[43] and *NTRK1*,[44] which have not been studied in bladder cancer. *CMYC* oncogene within 8q24 is known to be amplified in several tumors[45] and has been shown to be overexpressed in bladder cancer.[46] Amplifications and overexpression of oncogene *ERBB2* located at 17q21 have been shown to correlate with advanced TCC but not with survival.[34,47] Amplifications at 20q have been observed to correlate with poor prognosis in breast cancer and the region is known to harbor specific amplified genes (*AIB1*, *AIB3*, and *AIB4*). Several candidate genes are located at 20q, eg, the *PTP1B/PTPN1* gene (20q12), which is involved in growth regulation, and the *MYBL2* gene (20q13), which plays an important role in cell cycle progression. Moreover, the human cellular apoptosis susceptibility gene (*CAS*) has been mapped to this same region.[25] None of these genes has been studied in bladder cancer.

Losses of DNA copy number in 3p included 3p25, which contains the *VHL* tumor suppressor gene. Mutations in *VHL* have been described in the inheritable von Hippel-Lindau disease, sporadic renal cell carcinoma, mesothelioma, and small cell lung carcinoma.[48] However, *VHL* has not been studied in bladder carcinomas. Losses in 4q have been demonstrated in a large loss of heterozygosity of TCC and correlated with late progression.[35] No tumor suppressor genes have been identified on chromosome 4. The 5q losses detected in SCC span the *APC* locus (5q21-q22) that plays an essential role in colon cancer as well as in several other tumors.[49] Molecular studies have shown loss of heterozygosity at *RB1* locus (13q14) in TCC.[50] In addition, *ING1*, a candidate tumor suppressor gene, has recently been cloned and mapped to 13q34.[51,52] However, the minimal common overlapping region in our tumors was 13q21; therefore, there is a possibility of an unidentified tumor suppressor gene distal to *RB1*. Losses in 9p at the locus of tumor suppressor gene *p16* (9p21) were more frequent in SA-SCC.[53] Nevertheless, no tumor suppressor genes or oncogenes have been assigned to regions such as 4q and 5p, which are known to be affected in bladder cancer and other malignancies.

Conclusion

Our results show for the first time the genetic changes in SA and NSA tumors of the bladder and highlight the genetic changes underlying the development of SCC. Gains and high-level amplifications at 11q13 and 5p were related to SA-BC irrespective of the histological subtype. Some changes, such as losses in 3p and gains at 5p, were more frequent in SCC, whereas losses in 4q and 6q and gains at 17q were more frequent in TCC. Other changes and high-level amplifications occurred with indistinguishable frequencies between tumor subtypes, indicating that they may be involved in a common pathway for the development and progression of bladder tumors.

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