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Jumping Translocations Are Common in Solid Tumor Cell Lines and Result in Recurrent Fusions of Whole Chromosome Arms

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Jumping translocations (JTs) and segmental jumping translocations (SJTs) are unbalanced translocations involving a donor chromosome arm or chromosome segment that has fused to multiple recipient chromosomes. In leukemia, where JTs have been predominantly observed, the donor segment (usually 1q) preferentially fuses to the telomere regions of recipient chromosomes. In this study, spectral karyotyping (SKY) and FISH analysis revealed 188 JTs and SJTs in 10 cell lines derived from carcinomas of the bladder, prostate, breast, cervix, and pancreas. Multiple JTs and SJTs were detected in each cell line and contributed to recurrent unbalanced whole-arm translocations involving chromosome arms 5p, 14q, 15q, 20q, and 21q. Sixty percent (113/188) of JT breakpoints occurred within centromere or pericentromeric regions of the recipient chromosomes, whereas only 12% of the breakpoints were located in the telomere regions. JT breakpoints of both donor and recipient chromosomes coincided with numerous fragile sites as well as viral integration sites for human DNA viruses. The JTs within each tumor cell line promoted clonal progression, leading to the acquisition of extra copies of the donated chromosome segments that often contained oncogenes (*MYC*, *ABL*, *HER2/NEU*, etc.), consequently resulting in tumor-specific genomic imbalances. Published 2001 Wiley-Liss, Inc.†

INTRODUCTION

Jumping translocations (JTs) have been defined as nonreciprocal translocations involving a donor chromosome arm or chromosome segment fused to several different recipient chromosomes. The jumping translocation was initially described by Lejeune et al. (1979), whose analysis of chromosomes of a patient with Prader-Willi syndrome revealed that multiple copies of chromosome 15 were fused to the telomere regions of chromosome arms 5q, 8q, and 12q, subsequently forming three unbalanced translocations. A review of the literature reveals that JTs have been described in 135 patients with Crohn's disease, constitutional disorders, and hematological malignancies; in the latter they have been associated with a poor prognosis (Bernard et al., 2000). Chromosome arm 1q was identified as the most common donor in JTs, resulting in trisomies or tetrasomies for this chromosome arm (Sawyer et al., 1998; Busson-Le Coniat et al., 1999). Tanaka and Kamada (1998) performed FISH analysis on metaphase chromosomes and interphase nuclei from 141 leukemia and lymphoma patients. In 14 patients, the authors detected many copies of the identical small chromosome segments translocated to the telomere regions of several different recipient chromosomes. They coined the term "segmental jumping translocations" (SJTs) to refer to these unbalanced translocations that contributed to the copy number gains of numerous oncogenes (*MYC*, *BRC*, *ABL*, *MLL*, *AML1*, etc.). In solid tumors, jumping translocations have been reported for only one case, a squamous cell carcinoma derived from a xeroderma pigmentosum patient (Aledo et al., 1988).

The mechanism promoting the genesis of jumping translocations has yet to be determined. It has been suggested that the formation of JTs may be triggered by viral infections resulting in fusions between homologous virus-related sequences of different chromosomes (Andreasson et al., 1998). An alternative proposal has been made by Sawyer et al. (1998) regarding the formation of JTs observed in multiple myeloma cases. They reported that the heterochromatic regions underwent hypomethylation and decondensation, which consequently leads to increased recombination at the centromeric/pericentromeric regions of the chromosome arms 1q, 9q, 16q, and 19q.

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TABLE 1. Jumping Translocations Detected by SKY Analysis: Donor and Recipient Chromosomes/Segments*

Cell line tissue type	Jumping translocations donor chromosome/segment	Number of jumping translocations associated with each donor	Breakpoints of jumping translocations recipient chromosomes
BK-10	:14q11→14qter	4	**1(p12);** 8(p21);15(q12);t(**16q11;**11q;5q)
Bladder,	:15q11→15qter	2	**9(q34);** 19(p12)
transitional cell	t(:**16q11**→16qter::11q→::5q)	2	1(p12);7(q11.2)
carcinoma, grade III–IV	:22q11.2→22qter	2	**17(p11.2);** 20(q11.2)
5637	5pter→5p11:	4	i(5)(p10);**7(p12);21(q11.2);** 22(q11.2)
Bladder,	:17q11.2→17qter	3	4(q31); **11(p15);**15(q11)
carcinoma, grade	**:21q11.2**→21qter	2	3(q29); 22(q12)
II	**:Yq11.2**→Yqter	2	X(q12); **17(p11.2)**
J82	**:3q21**→3qter	2	**12(q13);16(p13.3)**
Bladder, carcinoma	4pter→4p11:	2	3(q11); 10(p11)
	5pter→5p11:	3	3(q11); i(5)(p10),14(q11)
	6pter→**6p21.3:**	3	11(q23); ins11(q23);dup 20(q13)
	:8p21→8qter	2	**3(p21);**21(q22)
	:14q11→14qter	2	13(q11);i(14)(q10)
	:15q11→15qter	2	9(p11);13(q11)
	:17q11→17qter	2	5(p11);**21(q11.2)**
	19pter→19p11:	3	14(q11);11(q11);**21(q11)**
	:Yq11.2→Yqter	2	4(p11);18(q23)
UM-UC-3	5pter→5p11:	2	**16(q11);18(q11)**
Bladder,	**:7q11**→7qter	2	10(q11);14(q11)
transitional cell	:14q11→14qter	4	**2(q11);** 8(q11);13(q11);15(q26)
carcinoma	20pter→20p11:	2	**12(q24.3); 16(p11)**
	:20q11→20qter	2	5(q33);8(p11)
	:21q11→21qter	2	X(q11);**3(p21)**
HT 1197	5pter→5p11:	2	i(5)(p10);8(q11)
Bladder,	**:5q31**→5qter	3	1(p13);**1(p36);10(q22)**
transitional cell	7pter→**7p11:**	2	dic 2(q37);dic**13(q14)**
carcinoma, grade III	:8q11→8qter	6	**1(q25);3(q21);3(p21);**i(8)(q10);12(q11); 17(p11)
	:11q→11qter	2	X(p11.2);6(p11)
	:15q11→15ter	2	1(q11);11(q11)
	17pter→**17p11:**	4	**Y(q11.2);**3(q11);8(p11);22(q11)
	:20q11→20qter	4	**6(p21.3);**16(q12.2);19(p12);22(q11)
DU-145	**:2q11**→2qter	2	15(q11); 18(p11)
Prostate,	:20q11→20qter	3	13(q11);15(q11);**18(q11)**
carcinoma	**:Yq11.2**→Yqter	2	15(q11);20(q11)
PC-3	:1q11→**1q21**::10q11→**10q23:**	3	3(p11);10(q23/hsr);15(q11)
Prostate,	3pter→**3p21:**	4	**1(p36);8(q24.3);**10(p11);10(q26)
adenocarcinoma	:3q11→3qter	2	10(q26);**17(q25)**
grade IV	**:3q21**→3qter	2	17(p13);17(q23)
	:4q11→4qter	2	6(p11);12(q11)
	:8q13→qter	7	**2(p24);**3(p11);3(p26);**12(q24);**14(q11); 14(q32);18(p11)
	:10q11→**10q23-24:**	3	**1(q21);** 15(q22);11(q11);
	:11q11→11qter	2	5(q11);18(p11)
	:15q11→15qter	3	**1(p11);**5(q11);13(q11)
	:17q21→17qter:	5	7(q11);14(q32);15(q13);19(q13);19(q13)
SK-BR-3	:1q11→1qter	4	5(p11);**3(p21);**6(q11);10(p11)
Breast,	:4q11→4qter	3	**1(p11);**14(q11);10(q11)
adenocarcinoma,	5pter→5p11:	3	1(q11);i(5)(p10);**21(q11.2)**
grade III	:6q11→6qter	2	3(q11);4(q11)
	:14q11→14qter	5	4(q11);5(p11);8(q11);9(q11);19(q11)
	20pter→20q13.3:	3	13(q32);**17(q25);17(q25)**
	:21q11.2→21qter	2	14(q11);22(q11)
	Xpter→Xq22:	4	5(q33);**8(q22);17(q21);**20(p11)
HeLa	:3q11→3qter	2	1(q11);12(q12)

(Continued)

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TABLE 1. Jumping Translocations Detected by SKY Analysis: Donor and Recipient Chromosomes/Segments* (Continued)

Cell line tissue type	Jumping translocations donor chromosome/segment	Number of jumping translocations associated with each donor	Breakpoints of jumping translocations recipient chromosomes
Cervix	5pter→5p11:	2	i(5)(p10);**5(p12)**
cervical,	:5q11→5qter	2	3(p11);22(q11)
adenocarcinoma	9pter→9p11:	3	**3(p21);**5(p11);i(9)(p10)
	:9q34→9qter	2	3(q25);**11(q22)**
	:15q11→15qter	2	4(q11);i(15)(q10)
	19pter→19p11:	2	7(q35);13(q11)
	:20q11→20qter	2	3(q11);i(20)(q10)
	:21q11→21qter	2	**1(p11);**15(q11)
Capan-1	5pter→5p11:	4	**7(q32);10(q22);10(q22);** 22(q13)
Pancreas,	**:5q31**→5qter	2	4(q33);**10(q22)**
pancreatic	:14q11→14qter	2	3(p11);**3(q21)**
adenocarcinoma	14q11.2→**14q24:**	4	17(q11);17(q11);22(q11);11(p15)
	:15q15→15qter	4	1(q23);4(q26);**6(q21);17(p12)**
	:17p12→17qter	2	11(q23);13(q12)
	:21q11→21qter	2	19(q11);20(q11)

*Breakpoints that appear in bold type are also viral integration sites.
[b]Breakpoints that have been underlined represent telomere regions of chromosomes.

Cytogenetic analysis of solid tumors often proves challenging, as their karyotypes contain highly rearranged chromosomes not fully resolved using conventional banding methods. With the advent of spectral karyotyping (SKY) (Schröck et al., 1996) and M-FISH (Speicher et al., 1996), many complex aberrations have been better characterized in various solid tumors and hematological malignancies (Knutsen et al., 2000; Schröck and Padilla-Nash, 2000). Comparative genomic hybridization (CGH) has proven particularly useful for mapping recurring tumor-specific chromosome imbalances in solid tumor genomes (Forozan et al., 1997; Knuutila et al., 1999; Ried et al., 1999). Despite the rare accounts of JTs in solid tumors in the literature, we hypothesized that JTs contributed to the acquisition and/or loss of specific chromosomal regions in carcinomas. We have utilized SKY and FISH to characterize 11 solid tumor cell lines with multiple aberrations, derived from epithelial tumors of the bladder, prostate, cervix, pancreas, and breast.

MATERIALS AND METHODS

Description of Cell Lines and Metaphase Preparation

Carcinoma cell lines derived from the bladder (transitional cell carcinomas, TCCs); BK-10, 5637, UM-UC3, HT 1197, J82, and RT4 (a primary papillary tumor, grade I), the breast (SK-BR-3), the cervix (HeLa), the pancreas (Capan-1), and the prostate (PC-3 and DU 145) were obtained from the American Type Culture Collection (ATCC; Manassas, VA). The culture conditions of the cell lines—except for BK-10 (Roberson et al., 1998)—are described by the ATTC. Cell lines were harvested for metaphase chromosomes by mitotic shake-off following Colcemid treatment (0.025 μg/ml, 1–4 hr). The cells were processed by standard cytogenetic methods using 0.075-M KCl and Carnoy's fixative (methanol:acetic acid, 3:1) as described by Modi et al. (1987).

The complete karyotypes for all 11 cell lines as determined by SKY and FISH analysis, and their derived chromosome ideograms, can be viewed on the Internet (www.ncbi.nlm.nih.gov/sky/skyweb.cgi). This database is part of the Cancer Chromosome Aberration Project (CCAP) website (http://www.ncbi.nlm.nih.gov/CCAP) sponsored by the National Cancer Institute (Kirsch et al., 2000). CCAP is designed to assist the scientific community to further characterize translocation breakpoints by integrating the data from cytogenetic and physical (structural) maps of the entire human genome, and by providing access to a panel of physically mapped sequence-ready DNA BAC clones (bacterial artificial chromosome) for every chromosome with a resolution of 1–2 Mb.

Hybridization Procedures

Preparation of SKY probes and methodology for slide pretreatment, hybridization, detection, and imaging were described by Macville et al. (1997). Prior to SKY and/or FISH, the slides were stored at 40°C for 1–2 weeks, pretreated with pepsin to remove excess cytoplasm, and postfixed in 1% formaldehyde in 1 × PBS/50-mM $MgCl_2$. The

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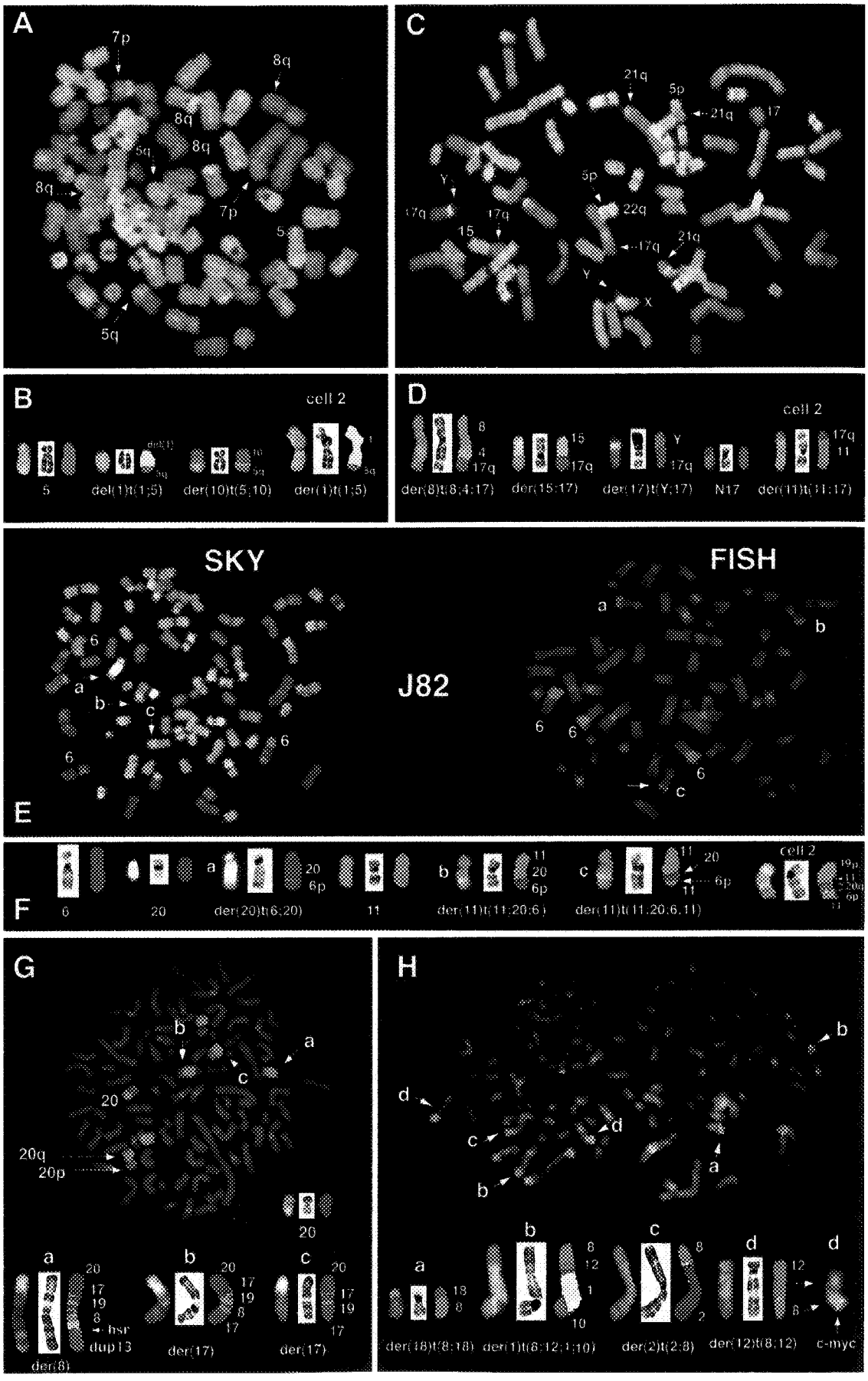

Figure 1.

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slides were then denatured for 1–2 min in 70% formamide/2 × SSC at 80°C and hybridized with SKY probes for 48–72 hr. Following hybridization, the indirect labels (biotin and digoxigenin) were detected with Avidin-Cy5 (Vector, Burlingame, VT), mouse antidigoxin (Sigma Chemical, St. Louis, MO), and sheep antimouse-Cy5.5 (Amersham Life Sciences, Arlington Heights, IL). Subsequently, the slides were counterstained with DAPI and mounted with *para*-phenylene-diamine antifade solution (Sigma). The chromosomal origin of the donor and recipient chromosomes for each jumping translocation was initially determined by SKY analysis. Small chromosome segments not identifiable by DAPI banding were further delineated by FISH analysis using chromosome arm paints, chromosome-specific centromere probes, loci-specific probes for 5p and 5q, and probes specific for the oncogenes and tumor suppressor genes *MYC*, *BCR*, *ABL*, *HER2/NEU*, *TP53*, and *RB* (Vysis, Downers Grove, IL).

Image Acquisition

SKY images were acquired with the SD200 SpectraCube system and analyzed using SKYView v1.2 software (Applied Spectral Imaging, Carlsbad, CA) (Schröck et al., 1996). The FISH images were acquired with Leica QFISH imaging software (Leica Imaging Systems, Cambridge, U.K.) using the custom designed filters TR-1, TR-2, TR-3, and Cy5 (Chroma Technology, Brattleboro, VT). Twenty metaphase cells were analyzed per cell line.

Statistical Analysis of JT Donor Chromosome Segments

The frequencies with which specific chromosome donor arms (e.g., chromosome arm 5p) associated with recipient chromosomes were evaluated for numerous recurrent jumping translocations with statistical methods using binomial probability tests by the Biostatistics and Data Management Section, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health.

RESULTS

JT Donor and Recipient Chromosomes

SKY revealed that 10 of 11 carcinoma cell lines exhibited 188 jumping translocations involving three to 10 different donor chromosome arms or segments per cell line. RT4, a cell line derived from a noninvasive papillary bladder tumor, did not exhibit any JTs. Table 1 summarizes the donor and recipient chromosomes associated with each JT found for each cell line, without differentiating the individual clones. Figure 1 provides examples of the JTs and SJTs revealed by SKY and FISH for five different tumor cell lines, representing the different categories of JTs (i.e., donor chromosome segment fusions to either centromeric/pericentromeric, intrachromosomal, or telomere regions of recipient chromosomes). A schematic summary of the donor chromosomes or segments involved in JTs and SJTs is presented in Figure 2A. Each cell line has its own identifying colored bar aligned to the right of the corresponding chromosome ideogram. All 10 cell lines contained multiple and different donor chromosome arms and/or segments. The numbers above the bars refer to the number of translocations observed involving the specific donor chromosome arm or segment in each individual cell line. The most prevalent donors were the acrocentric chromosomes 14 (18 JTs/5 cell lines), 15 (11 JTs/5 cell lines), and 21 (10 JTs/5 cell lines), and chromosome arms 5p (20 JTs/7 cell lines) and 20q (11 JTs/4 cell lines). SK-BR-3 (breast) was the only cell line with chromosome arm 1q as a donor. DU-145 (prostate), UM-UC-3 (bladder), and 5637 (bladder) differed from the other seven cell lines in that all their donor segments consisted of whole chromosome arms. Eight out of 10 cell lines had donor chromosomes/segments translocated to the telomere regions of the recipient chromosomes. One cell line in particular, prostate cell line PC-3, had telomere fusions involving the chromosome donor segment 8q13→8qter, which was fused to the telomeres of three different recipients, as well as one intrachromosomal fusion, and fusions of the

Figure 1. Spectral karyotypes and FISH analysis of JTs and SJTs in solid tumor cell lines. **A:** Three JTs detected in bladder cancer cell line HT1197 as revealed by SKY analysis involving the donors 7p, and 8q, and the SJT 5q31→qter. **B:** The SKY classifications and companion inverted-DAPI images for the different SJT involving 5q31. **C:** The SKY image for bladder cancer cell line 5637 (clone C). Four JT donors are identified (arrows): 5p, 17q, 21q, and Yq. **D:** The SKY classification of the JTs involving the 17q donor. **E:** The SKY (left) and FISH (right) images for bladder cancer cell line J82. Arrows indicate the donor segment derived from chromosome 6 in three different SJTs (a, b, and c). This segment was further delineated using the chromosome arm paint for 6p (red signal). **F:** An enlargement of the SKY classification of four different SJTs in J82, as well as the normal chromosomes 6, 11, and 20. **G:** A metaphase spread from breast cancer cell line SK-BR-3. One of its JT donors consisted of an entire chromosome 20 as revealed by FISH using arm paints for 20p (red signal) and 20q (green signal). The centromere appears inactive in chromosome 20, as there is no constriction. The SKY classification of three JTs (a, b, c) is shown below. **H:** The donor segment 8q13→qter (SJT) appears as a red signal in prostate cancer cell line PC-3. The yellow signal identifies the oncogene *MYC* (8q24). This SJT was found by SKY analysis in seven unbalanced translocations, four of which are shown below (a, b, c, and d).

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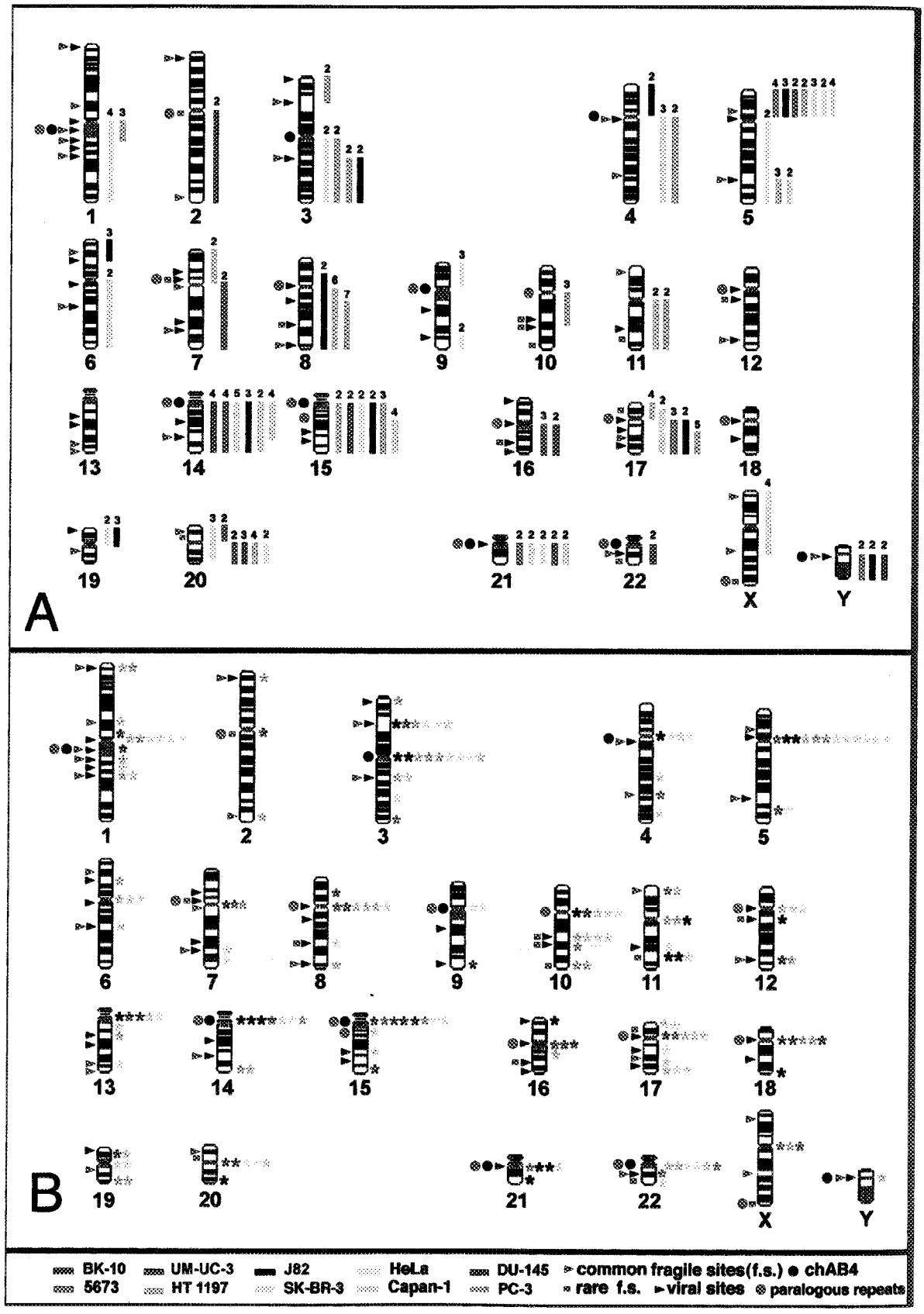

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8q13 segment to the centromeric region of three additional recipient chromosomes. This SJT contributed to multiple copies of the oncogene *MYC*, as shown in Figure 1H. Two cell lines (bladder 5637 and prostate DU-145), which had been reported as having lost the Y chromosome (cell line descriptions in ATTC), were found to contain the Y chromosome as the donor in JTs. Chromosomes 12, 13, and 18 did not participate as donor segments.

Various donors of the JTs and SJTs did not consist of single chromosome arms or segments but rather fusions of rearranged chromosomes. For example, one donor in bladder cancer line BK-10 was derived from translocations of the long arm of chromosome 16, the long arm of chromosome 11, and the long arm of chromosome 5 as determined by FISH (Padilla-Nash et al., 1999). Prostate cancer cell line PC-3 contained a donor composed of the fusion of a portion of the long arm of chromosome 1 with a portion of the long arm of chromosome 10. This fusion donor segment participated in three different JTs. In addition, another unbalanced translocation contained an amplification of this donor segment as revealed by FISH using arm paints for 1q and 10q (data not shown). The JTs observed in breast cancer cell line SK-BR-3 included one donor that was atypical of other JTs found in this study. It consisted of both arms of chromosome 20 as discerned by FISH analysis (Fig. 1G). The telomere region of the long arm of chromosome 20 (20q) was fused to the centromere/pericentromeric regions of the recipient chromosomes. Probes for the subtelomere region of 20q were hybridized to SK-BR-3 to determine the presence or absence of these specific sequences. Contrary to what has been observed in JTs from hematological malignancies, the subtelomere region was maintained in all the JT's involving 20q and the normal copies of chromosome 20 (data not shown).

Recurrent Jumping Translocations

All recurrent JTs consisted of isochromosomes, whole-arm chromosome rearrangements, and/or fusions of acrocentric chromosomes (Table 1). The donor chromosome arm 5p was associated with 20/188 JTs. Five of the 10 cell lines had the recurrent aberration i(5)(p10), and at least two cell lines had the recurrent translocations der(5)t(5;21)(q11.2;q11.2), der(14)t(13;14)(q11.2;p11.2), der(5)t(5;14)(q11.2;q11.2), der(22)t(21;22)(q11.2;p11.2), and der(22)t(20;22)(q11.2;p11.2) (Table 1). The acrocentric chromosomes 13, 14, and 15 were also frequent recipients (six, seven, and eight JTs, respectively). Chromosome arms 11p or 12p were never involved as recipients in any JTs.

Statistical analysis revealed that the frequent occurrence of chromosome arm 5p within the JTs observed in this study was a nonrandom event. The probability that 5p became fused to recipient chromosomes in 20 JTs by chance was determined to be $P \leq 0.0000013$ based on the premise that there is an equal probability of any chromosome arm being involved in a whole-arm JT at any point in time.

Donor and Recipient Breakpoints

Seventy-two percent (136/188) of the donor breakpoints occurred in the centromere regions (Fig. 2A). The total number of JTs with breakpoints in the telomere regions of recipient chromosomes was minor (12%, 23/188) relative to centromere fusions (60%, 113/188). Neither Du-145 (prostate) nor HeLa (cervix) had donor segments joining to the telomere regions of the recipient chromosomes. With respect to the JTs found in five cell lines that involved 14q as the donor, only two 14q JTs, der(3)t(3;14)(q21;q11.2) from the pancreas cell line Capan-1 and der(15)t(14;15)(q11.2;q26) from the bladder cell line UM-UC-3, did not consist of fusions between centromere regions of

Figure 2. Summary of donor segments and recipient chromosome breakpoints in jumping translocations present in 10 solid tumor cell lines. **A:** The total JTs and SJTs revealed by SKY/FISH analysis for each cell line. Each specific chromosome arm/segment comprising the JT donors are shown as vertical bars to the right of the chromosome ideogram and are color-coded by cell line. The numbers above the bars indicate the frequency with which each donor is associated with the JTs described in Table 1. **B:** A summary of the breakpoints found for each recipient chromosome in every JT in 10 cell lines. To the left of the ideograms in both A and B are breakpoints that are correlated to the locations of viral integration sites for eight DNA viruses (black arrows); common and rare fragile sites (red arrow and red squares, respectively); chAB4/multisequence gene families (black circles); and paralogous repeats (red circles) that have been reported as hot spots for recombination. Not all published locations of fragile sites are shown here. The following is a partial list of the DNA viral sites with their accompanying references. HTLV-1: 4p15, 4q12, 6p21, 6p23, 6q12–13, 9q21, 15q24, 16p13, 16q22 (Glukhova et al., 1999); HIV-1: 2p21, 7p13, 17q21, 19p13 (Glukhova et al., 1999); Adenovirus: 1p35–ter, 1q42, 17q21–22 (Popescu et al., 1990); EBV: 1p31, 1p35, 1q31, 4q22–25, 6p21, 7q22, 13q21, 14q21, 21q11–12; HBV: 1p11–12, 3p22–24, 8q13, 10q22.1, 11p13–14, 11q22, 15q22, 16p11–16q11, 17p11.2–12, 17q22–25, 18q11.1–q12, Yq12 (Popescu et al., 1990; Pineau et al., 1998); SV-40: 7q31; HPV type 16: 2p24, 3p14.2, 7p11–p13, 8q24 (Popescu et al., 1989; Smith et al., 1992); HPV type 18: 3p21, 3p25, 5p12, 8q21–22.3, 8q23–24, 9q31–34, 10q23–24, 12q11–13, 12q24, 13q14, 18q11.1, 22q12 (Popescu et al., 1989; Smith et al., 1992); HSV: 1p34, 1p31–32, 1p22, 1q12, 1q21, 1q25, 1q32, 1q42, 2p21, 2p23, 2q31, 2q33, 3p21, 4q31, 5q31, 6q21, 7p15, 7p13, 7q22, 7q32, 8q22, 9q32, 11p13, 12q24, 13q14, 14q24, 15q22, 16q24, 17q22, 18q21 (De Braekeleer et al., 1992).

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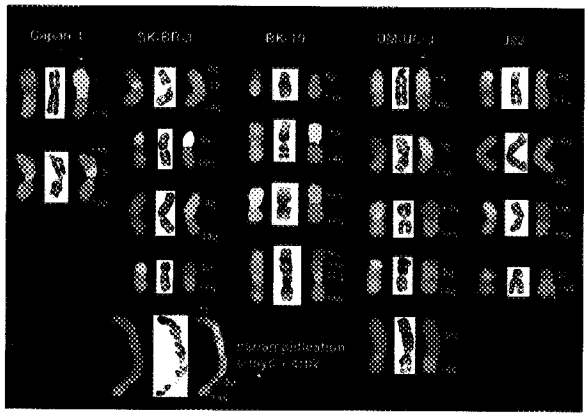

Figure 3. Summary of jumping translocation involving 14q as the donor. With the exception of 2 JTs (asterisks), 18 JTs consisted of centric fusions of acrocentric chromosomes or chromosome arms. A recurrent JT, the der(13;14), was found in the two bladder cancer cell lines UM-UC-3 and J82. The complex marker in breast cancer cell line SK-BR-3 (arrow) was revealed by FISH to contain amplifications of the oncogenes *MYC* and *HER2/NEU* (data not shown).

TABLE 2. Recipient Chromosome Breakpoints: Correlations to Viral Integration Sites and Fragile Sites

Cell line	Recipient breakpoints	Viral sites	Common fragile sites	Rare fragile sites
BK-10	10	4	1	1
5637	11	5	4	0
J82	23	6	1	3
UM-UC3	14	6	2	1
HT1197	25	8	7	1
DU-145	7	1	0	0
PC-3	33	7	7	4
SK-BR-3	26	7	3	0
HeLa	19	5	1	0
Capan-1	20	6	4	5
Total	188	55 (29%)	30 (16%)	15 (8%)

both donor and recipient chromosomes (Fig. 3). The three most common breakpoints within the recipients are 5p11–5q11 (12 JTs, 6 cell lines), 3p11–3q11 (9 JTs, 6 cell lines), 15p11–q11 (9 JTs, 6 cell lines), and 1p11–1q11 (9 JTs, 4 cell lines).

Viral Integration Sites and Fragile Sites

The 188 JT breakpoints detected by SKY and FISH for both donor and recipient chromosomes were compared to previously reported cytogenetic locations of viral integration sites for eight DNA viruses: HSV, HIV-1, HTLV-1, Adenovirus, HBV, EBV, HPV-16, and HPV-18 (Popescu et al., 1990; Smith et al., 1992; Glukhova et al., 1999). Representative numbers of common and rare fragile sites (Sutherland and Simmers, 1988) are displayed next to the chromosome ideograms. Table 2 correlates the numbers of breakpoints in the recipient chromosomes to known locations for fragile sites, both common and rare, and viral integration sites. Breakpoints of donor segments correlated with a higher frequency to viral integration sites (74/188, 39.4%) than to fragile sites (39/188, 21%). Additionally, 35 JT breakpoints coincided with both viral and common/rare fragile sites, 28 of which were concentrated in intrachromosomal regions (Fig. 2B).

Chromosome Copy Number Gains

All the solid tumor cell lines analyzed in this study had complex karyotypes with multiple chromosomal aberrations. SKY and FISH analyses revealed that unbalanced translocations were the predominant class of chromosome abnormalities in these cell lines. Fifty-six percent (106/188) of all jumping translocations consisted of whole-arm translocations (Table 3). In addition, jumping translocations provided the largest category of unbalanced translocations (except in the bladder cell line RT4). Our analysis revealed the presence of 11 different donor segments in 43 segmental jumping translocations: 1q11→1q21::10q11→10q23 (PC-3), 3pter→3p21 (PC-3), 3q21→3qter (PC-3, J82), 5q31→5qter (Capan-1, HT1197), 8q13→8qter (PC-3), 9q31→9qter, 10q11→10q23-24 (PC-3), 14q11→14q24 (Capan-1), 15q15→15qter (Capan-1), 17q21→17qter (PC-3), and Xpter→Xq22 (SK-BR-3), all of which resulted in copy number gains of these specific chromosome regions relative to the ploidy of the cell. With respect to the donor segments involving whole chromosome arms, only chromosome 21 resulted in a balance (i.e., neither a loss nor a gain) of chromosome copy numbers for cell lines HeLa, SK-BR-3, UM-UC-3, and 5637 (in 3/4 clones), whereas in Capan-1 there was loss of 21q, as shown in Table 3, which summarizes the ploidy, chromosome number, and characterization of the structural aberrations of the 11 solid tumor cell lines analyzed by SKY. The majority of the structural aberrations were unbalanced translocations, as opposed to deletions. Of the total translocations observed for each cell line, jumping translocations comprised the major category. For example, pancreatic cancer cell line Capan-1 had 36 structural aberrations, 78% of which were translocations, and 71% of these were jumping translocations. In SK-BR-3, 80% of the structural aberrations consisted of translocations, with 56% of those being jumping translocations.

Many of these tumor cell lines were multiclonal, and often some of the donor chromosomes remained fused to the same recipient chromosomes in the different clones. However, it was more com-

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mon to observe a donor chromosome segment fused to different recipients in different cells. Bladder tumor 5637 is a good example: while the donor 21q was associated with the same three recipients (3qter, 22q, and 5p) in four different clones, the donor chromosome arm 5p, fused with four different recipients (all in the centromeric/pericentromeric region) in three out of four clones, contributing to a gain of copy number for 5p in all clones. Analysis of the multiple JTs in each clone made it possible to trace the progenitor clone and follow the course of clonal progression in a tumor, as is illustrated for bladder cell line 5637 in Figure 4.

DISCUSSION

Jumping translocations are considered rare cytogenetic aberrations and have been reported predominantly in constitutional disorders and hematological malignancies. Most JTs have been described as the fusion of a donor segment to the telomere regions of different recipient chromosomes, resulting in nonreciprocal translocations and trisomy or tetrasomy of the donor segment (Bernard et al., 2000). In contrast, Sawyer et al. (1998) detected recurring whole-arm JTs (centromere fusions of two chromosome arms) involving the chromosome arm 1q fused to chromosome arms 16q and 19p in 36/158 patients with multiple myeloma and complex karyotypes.

In the present study, SKY and FISH analysis unveiled multiple JTs in 10 of 11 solid tumor cell lines, indicating that JTs are also prevalent in established cell lines derived from carcinomas. Telomere fusions were in the minority in our solid tumor cell lines and accounted for only 23/188 (12%) of the JT fusion events. The majority of the chromosome associations in the solid tumor JTs resulted from the recombination of centromeric/pericentromeric regions of both donors and recipients, yielding whole-arm unbalanced translocations. Overall, unbalanced translocations were the most common type of structural aberrations in the 10 cell lines analyzed by SKY, with JTs being a significant component of the total translocations detected (Table 3).

The most frequent donor segments were the acrocentric chromosomes 14, 15, and 21, and chromosome arms 5p and 20q. In contrast, the donor segments reported in JTs from patients with hematological disorders are primarily 1q11, 1q21, 1q23, 3q13, 3q21, 11q23, and 15q11 (Bernard et al., 2000). In the majority of JT reports, only one donor chromosome segment is observed. Tanaka and Kamada (1997) performed FISH analysis using probes for various oncogenes on 141 leukemia/lymphoma patients. Fourteen patients exhibited JTs, and only two of these patients had multiple copies of two different chromosomal regions, those harboring the oncogenes *ABL* (9q34) and *MLL* (11q23), within the same cell. In our study, we observed as many as 10 different donor segments in two different cell lines, bladder J82 and prostate PC-3. In addition, PC-3 (prostate) and Capan-1 (pancreatic adenocarcinoma) each had two different donor segments derived from the same chromosome (3q11→qter, 3q21→qter, 14q11→qter, 14q11→14q24, respectively), which had recombined to different sets of recipient chromosomes. These types of fusion events for JTs have not been reported previously, but have also been observed in low-passage primary cultures of murine mammary tumors derived from *BRCA-1* conditional knockout mice (Z. Weaver, personal communication).

One mechanism postulated for the genesis of the JTs observed in constitutive disorders and hematological malignancies is the loss of telomere function (LTF), as shown by the FISH analysis of JTs in patients with Prader-Willi syndrome and B-cell non-Hodgkin's lymphoma using chromosome-specific telomere probes (Gray et al., 1997; Vermeesch et al., 1997). The authors found deletions of the telomere repeat sequences (TTAGGG) in the recipient chromosomes. Hatakeyama et al. (1998), using Southern blot hybridizations and DNA sequence analysis, demonstrated that in a leukemia patient with JTs, the normal telomere sequences in the recipient chromosome were deleted and replaced by variant subtelomeric sequences. The authors speculated that deletions at the telomeres enabled the recipient chromosomes to become targets for recombination with other deleted chromosomes.

Another mechanism implicated in the formation of JTs is described by Sawyer et al. (1998). They postulated that the whole-arm JTs found in multiple myeloma patients were created by hypomethylation of the DNA in the pericentromeric regions of chromosomes. This resulted in decondensation, which promoted breakage and recombination between chromosomes with large amounts of heterochromatin in their centromere/pericentromeric regions, such as chromosomes 1, 9, 16, and 19.

The occurrence of multiple JTs involving centromere fusions of whole chromosome arms may be inherent in the DNA structure of centromere regions and serve as a potential mechanism for the genesis of JTs. The pericentromeric regions of chromosomes 1, 2, 8, 9, 14, 15, 16, 17, 18, 21, and 22 are known to encompass multigene families, such as the variable immunoglobulin genes, the keratin-

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TABLE 3. Summary of Cytogenetic Analysis of 11 Cancer Cell Lines*

Cell line	Ploidy	Chromosome number	Structural aberration	Total translocations, reciprocal vs. unbalanced	Jumping translocations	Whole chromosome gains and losses	Chromosome arm/segment copy number losses	Chromosome arm/segment copy number gains
BK-10								
Clone A	± 4n	83–102	19	1/14	6	−2,−4,−10,−16,−17,−21 +7,+9[a],+18,+20	−6q,−7p,−8p	+1q,+3q,+5p, +11q,+13q, **+15q,**+19p,**+22q** +8q24>ter
Clone B	± 4n	83–102	21	1/16	7	−10,−16,−17,−21 +9[a],+20	−2q,−4q,−6q,−8p,−14q	+1q,+3q,+5p,+11q, +13q,+15q,+19p,+22q
5637								
Clone A	< 3n	63	13	1/9	6	−4,−10,−12,−16,−18 +7,+20	−2q,−17p −8pter→8p21	**+5p,**+9q,+13q,**+17q,** +5q33→qter,
Clone B	< 3n	65	13	1/11	6	−10,−12,−16 +7,+20	−17p −4pter→q25, −4q33→qter, −5q11→q33, −8pter→p21	**+5p,**+9q,+13q,**+17q,** +4q25→q33, +5q33→qter, +22q12→qer
Clone C	< 3n	65	15	1/13	7	−10,−12,−16 +7,+20	−17p,−Xp −4pter→q25, −4q33→qter, −5q11→q33, −8pter→p21	**+5p,**+9q,+13q,**+17q,** +18p,**+Yq** +4q25→q33, +5q33→qter, +22q12→qer
Clone D	< 3n	63	14	1/12	8	−5,−10,−12,−16 +7,+20	Same as C	Same as C
J82								
Clone A	< 3n	68	21	19	5	−21 +13,+20,+Y	−2p,−3p,−4q,−10q, −17p,−19q	+3q,**+4p,+5p,**+10p, **+15q,+19p,**+20q **+3q21→3qter, +6pter→6p21, 8p21→8qter**
Clone B	< 6n	140	42	22	14	Idem	Idem	Idem
UM-UC 3	> 3n	80	29	24	14	−1,−4,−17,−19 +12,+20	−2p,−4q,−16p,−18q	+Xp,+3q,**+5p,+7q,**+6q, +8q,+10q,+11q,+13q, +12p,+13q,**+20p, +20q,**+22q
HT 1197	+ 3n	83	33	21	8	−13,−15,−16 +12,+21,+22,+Y	−3p,−4q,−6q,−7q,−8p, −16q,−18q, −10q22→qter	+1p,**+5p,**+6p, **+7p,+11q,+14q,**+16q,+20p, **+20q**
RT4								
Clone A	± 2n	44	5	4	0	−16,−18 +15	−6q25→qter	+12pter→q22,+15q26 →qter,+19pter→p13.1

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						−18,−18 +15	−6q25→qter	+12pter→q22,+15q26 →qter,+19pter→p13.1
Clone B	±4n	89	5	3	0	−13,−16,−21 +14,+15	−10p,−17q, −1p36→pter,−6q25 →qter, −8p21→pter	+8q,+17q, +15q26→qter, +19pter→p13.1
SK-BR-3	>3n	80	30	24	16	−18, +7,+11,+12,+17,**+20**	−2q,−4p,−6p,−8p−12p, −17p,−19p	**+1q,**+3q,**+4q,+5p,+8q,** +9q,**+14q,**+15q,+16p, +19q,**+Xpter→q22,** +5q31→qter, +10pter→q22, +13q22−qter
HeLa								
Clone A	>3n	76–78	27	23	9	+1,+15,+17	−20p,−11q23→qter, −13q14→qter, −22q13→qter	+3q,**+5p,+9p,** +12p,+16p, **+20q,+3q21→qter,** +8q24→qter, **+9q34→qter,** +22q11→qter
Clone B	>3n	80	23	17	6	idem	idem	idem
Capan-1	<3n	57	36	28	20	−4,−6,−12,−13,−18, **−21,**−22,−Y +3,+7,+15	−9p,−12p,−16p,−17p, −18q,−20p −5q11→q31,−8pter →8p21,−7q22→qter, −9q34→qter,−10q23 →qter,−17q25→qter	+2q,**+5p,**+8q,+11q, +18p **+5q31→qter** **+14q12→q24,** **+15q15→qter,** **+17p12→q25**
PC-3	<3n	61	21	20	12	−4,−6,−7,−9,−16, −19,−22,−Y +18,+20,+21	−6q,−7q,−8p,−10p,−11p, −12p,−17p −1q21→qter	**+5p,+11q,+14q,+15q,** +18p **+17q21→qter** **+1q11→q21,** **+3pter→p21** **+8q13→qter** **+10q11→q23**
DU-145								
Clone A	<3n	60	20	17	7	−3,−4,−13,−22	−1p,−2q,−6q,−8p,−9p, −11p,−12p,−16p, −19q,−20p	+5p,+8q,+14q,+17q, **+20q,+Yq**
Clone B	>6n	146	69	30	15	−3,−4,−7,−9,−10,−18, −19,−21,−22 +5	−1p,−8p,−9p,−11p, −12p −16p,−17p,−19q,−20p	**+2q,**+5p,+8q,+11q, +12q,+13q,+17q, +19p,**+20q,+Yq**

*Bold lettering refers to chromosome arms/segments involved in JTs.
[a]All copies of chromosome 9 contain deletions for p16 (Padilla-Nash et al., 1999).

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Figure 4.

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ocyte growth factor gene (*KGF*), and the chAB4 multisequence gene families (Wöhr et al., 1996). These genes contain duplications of unique low copy repeat sequences, referred to as paralogous sequences, and portions of these genes have been shown to be located in many different sites within the genome (Eichler, 1998; Horvath et al., 2000). They have been implicated in generating hot spots for recombination and resulting in translocations specifically associated with microdeletion syndromes. As depicted in Figure 2, breakpoints for both donor and recipient chromosomes in our study were predominantly located within these sites.

The frequent association of chromosome arm 5p in our solid tumor JTs (20/188 JTs) was determined to be a nonrandom event by statistical analysis. A review of recurrent chromosomal rearrangements in human neoplasias by Mitelman et al. (1997) showed that breakpoints within the centromere region (5p10 and 5q10) of chromosome 5 are common in carcinomas of the breast, kidney, colon, lung, ovary, pancreas, stomach, and bladder. Recently, a 4.6-Mb map was established for the centromeric region of chromosome 5 by using 46 nonchimeric YAC (yeast artificial chromosome) clones. Both the p-arm and q-arm proximal sides of the centromere of chromosome 5 were found to contain blocks of alpha satellite sequences bordered by repetitive L1 elements (LINE-1, retrotransposons), which are unlike those of any other human chromosomes examined to date (Puechberty et al., 1999). L1 elements have been implicated in generating duplications and deletions within heterochromatic regions, thereby affecting the integrity of centromeres (Laurent et al., 1999; Kazazian, 2000).

In addition to the LTF, hypomethylation, and/or genomic instability found within centromere/pericentromeric regions, there is also the hypothesis that jumping translocations originate from the recombination between homologous chromosome regions containing viral DNA sequences that have integrated into the human genome. Hoffschir et al. (1992) reported that jumping translocations occurred in human fibroblasts infected with the virus SV-40, and increased breakage has been detected in chromosomes from AIDS-related non-Hodgkin's lymphomas, yielding multibranched derivative chromosomes (involving donor 1q) fused to telomeres of recipient chromosomes (Bartoli et al., 1996). In our study, 39% of the donor breakpoints and 30% of the breakpoints within the recipient chromosomes are concentrated in known viral integration sites, as determined by cytological observations of chromosomes at the 400–500 band level (Table 2). For example, the 6p21 breakpoint seen in bladder cancer cell lines HT1197 and J82 is associated with the HTLV-1 viral integration site (Glukhova et al., 1999). The 8q13 and 10q22 breakpoints, involved in seven and three JTs, respectively, in the prostate cancer cell line PC-3, are viral integration sites for HBV (Pineau et al., 1998). Some recipient chromosome breakpoints, including 3p21 (J82, UM-UC-3, HT1197, SK-BR-3, and Capan-1) and 3q21 (J82, HT1197, PC-3, and Capan-1), are not only viral integration sites but are regions to which common and rare fragile sites have been mapped and are often associated with translocation breakpoints for various neoplasms (Peters, 1990; Popescu et al., 1990).

Everett et al. (1999) demonstrated by interphase FISH and immunofluorescence analysis of centromeres that viral infections by Herpes simplex type 1 altered the proteins (Vmw110) bound to the centromeric protein CENP-C, thereby preventing the proper attachment of kinetochores that disrupted chromosome segregation and significantly delayed mitosis, as well as inducing chromosome breakage.

Figure 4. SKY karyotypes of bladder 5637 clones and likely sequence of clonal progression. Bladder cancer cell line 5637 has four distinct but related clones. The JTs detected by SKY analysis are marked by yellow asterisks. The donor chromosome arms 5p, 8q, 17q, 21q, and Yq are involved in numerous JTs in every cell, but the donors changed partners (recipients) from one clone to the other. Based on the presence or absence of all structural aberrations and normal chromosomes, the clones were arranged in the putative order of tumor progression. There are no normal copies of chromosome 21 in this cell line, but the 21q donor is found in three different JTs in the four subclones. The karyotypes for each subclone of 5637 are as follows. **Clone A:** 63,XXY, del(2)(q31),der(3)t(3;21)(q29;q11.2),der(3)t(3;hsr;6)(3qter→p11.2::6p?::3p?:6p?::3p?::6p?::3p::6p?::3p::6q12qter),−4,t(4;8)(q25;p21),+der(5)t(5;21)(q11.2;q11.2),+7, i(8)(q10),+del(9)(p22),−10,der(10)t(5;10)(q33;p15)x2,der(11)t(11;17)(p15;q11.2),−12,i(13)(q10),der(15)t(15;17)(p11.2;q11.2),−16,−17,−18,+20,−21,−21,der(22)t(21;22)(q11.2;q12)[cp4]. **Clone B:** 65,XX,der(Y)t(Y;17)(p11.2;q11.2), der(3)t(3;21)(q29;q11.2),der(3)t(3;hsr;6)(3qter→p11.2::6p?::3p?:6p?::3p?::6p?::3p::6p?::3p::6q12qter),−4,t(4;8)(q25;p21),+der(5)t(5;21)(q11.2;q11.2),+7, der(8)t(4;8)(q25;p21)t(4;17)(q31;q11.2),+del(9)(p22),−10,der(10)t(5;10)(q33;p15)x2,−12,i(13)(q10),der(15)t(15;17)(p11.2;q11.2),−16,i(17)(p10) ,+20,−21,−21,+der(22)t(21;22)(q11.2;q12)[cp4]. **Clone C:** 65,X,der(Y)t(X;Y)(q11.2;p11.2),der(Y)t(Y;17)(p11.2;q11.2),der(3)t(3;21)(q29;q11.2),der(3)t(3;hsr;6)(3qter→p11.2::6p?::3p?:6p?::3p?::6p?::3p::6p?::3p::6q12>qter),−4, t(4;8)(q25;p21),i(5)(p10),+der(5)t(5;21)(q11.2;q11.2),+7,der(8)t(4;8)(q25;p21)t(4;17)(q31;q11.2),+9,−10,der(10)t(5;10)(q33;p15)x2,−12,i(13)(q10),der(15)t(15;17)(p11.2;q11.2),−16,i(17)(p10) ,i(18)(p10),+20,−21,−21,+der(22)t(21;22)(q11.2;q12)[cp3]. **Clone D:** 63,X,der(Y)t(X;Y)(q11.2;p11.2),der(Y)t(Y;17)(p11.2;q11.2),der(3)t(3;21)(q29;q11.2),der(3)t(3;hsr;6)(3qter→p11.2::6p?::3p?:6p?::3p?::6p?::3p::6p?::3p::6q12>qter),−4,t(4;8)(q25;p21),der(5)t(5;21)(q11.2;q11.2), +der(7)t(5;7)(p12;q11.2), der(8)t(4;8)(q25;p21)t(4;17)(q31;q11.2),+9,−10,der(10)t(5;10)(q33;p15)x2,−12,i(13)(q10),der(15)t(15;17)(p11.2;q11.2),−16,i(17)(p10) ,i(18)(p10),+20,−21,−21,+der(22)t(21;22)(q11.2;q12)t(7;22)(q11.2;qp11.2),[cp3].

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Therefore, it is not inconceivable that viruses preferentially cause breakage at the centromeric areas and potentially generate JTs.

The evidence that JTs play an important role in specific chromosome copy number gains and losses associated with tumor progression comes from the analysis of the TCC bladder cell line 5637, which has four subclones. Donors involving chromosome arms 5p and 17q contributed to 5p and 17q gains in all four subclones, as shown in Figure 4. The emergence of unique JTs involving these same donor chromosome arms within each clone provided a pattern that defined the course of clonal progression within this cell line. As JTs appeared, normal copies of chromosomes 5, 7, and 17 disappeared, suggesting that the jumping translocations were derived from fission of normal chromosomes within their pericentromeric/centromeric regions. In the most advanced clone, copies of the short arm of chromosome 17 were lost, reducing the total copy numbers of the tumor suppressor gene *TP53* (17p13). Interestingly, no normal copies of chromosome 21 were present in any of the four subclones, whereas the donor 21q was found in the three unbalanced translocations: der(3)t(3;21), der(5)t(5;21), and der(22)t(21;22). Therefore, the overall chromosome copy number for chromosome 21 remained balanced.

The JTs and SJTs found by SKY in the five bladder tumors (BK-10, 5637, J82, UM-UC-3, and HT1197) revealed gains of specific donor chromosome arms/segments similar to those observed in a CGH study of bladder carcinomas by Koo et al. (1999) (Table 3). The authors analyzed 14 patients with invasive transitional cell carcinoma (TCC) and 2 with noninvasive papillary tumors, using conventional cytogenetic analysis and CGH. They found chromosome gains of chromosome arms 1q, 3p/q, 5p, 6p/q, 7p, 8q, 11q, 12q, 13q, 17q, 18q, 20p/q, and the X chromosome in the TCC tumors, whereas no specific chromosome gains or losses were seen in the two noninvasive papillary tumors.

Recent advances in sequencing the entire genomes from various organisms have demonstrated that there still remains a great deal to learn about the role of the heterochromatin located in the centromeres. Fang-Lin et al. (2000) analyzed the heterochromatic regions of the fourth chromosome in *Drosophila melanogaster*, which was once thought to be devoid of active genes. They determined by FISH using cosmid and BAC clones that the banded regions consisted of middle repetitive DNA sequences interspersed with V domains (heterochromatin-like) and R domains (euchromatin-like) and contained 50–75 active genes. In *Drosophila*, it has been shown that the translocation of genes (e.g., white locus) normally found in euchromatin to heterochromatic regions can result in gene silencing; therefore it is not improbable to conclude that JTs may relocate genes important for tissue-specific tumorigenesis, as many of the solid tumor donor breakpoints were adjacent to pericentromeric regions, which have been shown to be gene-rich, in particular 17p11.2 and 22q11.2.

While we cannot discern whether or not JTs represent early or late events in tumorigenesis, the consequences of JTs are the acquisition of additional copies of chromosome arms 3q, 5p, 8q, 14q, 15q, 17q, and 20q, which mirrors the patterns of chromosome imbalances described in previously published CGH analysis from all tissue types (Knuutila et al., 1999; Ried et al., 1999), and in particular the carcinoma cell lines Hela, Capan-1, Du-145, PC-3, and SK-BR-3 (Ried et al., 1997; Ghadimi et al., 1999; Macville et al., 1999).

In conclusion, jumping translocations are not confined to hematological malignancies but also occur in cell lines derived from a variety of epithelial tumors from various organs. The breakpoints associated with JTs appear to be associated predominantly with centromere regions. There is a nonrandom distribution of breakpoints located in close proximity to previously reported viral integration sites and fragile sites. The overall pattern of JTs detected in the solid tumors is far more complex than those found in the hematological malignancies. JTs resulted primarily in gains of multiple chromosome arms and in most instances coincided with tissue-specific chromosome arm gains and losses as observed by CGH analysis. Therefore, jumping translocations may constitute an as yet unrecognized mechanism that contributes to the emergence of a tumor-specific pattern of genomic imbalances.

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