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Mapping of 262 DNA Markers into 24 Intervals on Human Chromosome 11

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Summary

We have extended our mapping effort on human chromosome 11 to encompass a total of 262 DNA markers, which have been mapped into 24 intervals on chromosome 11; 123 of the markers reveal RFLPs. These clones are scattered throughout the chromosome, although some clustering occurs in R-positive bands (p15.1, p11.2, q13, and q23.3). Fifty-two of the markers were found to contain DNA sequences conserved in Chinese hamster, and some of these 52 also cross-hybridized with DNA from other mammals and/or chicken. As the length of chromosome 11 is estimated at nearly 130 cM, the average distance between RFLP markers is roughly 1 cM. The large panel of DNA markers on our map should contribute to investigations of hereditary diseases on this chromosome, and it will also provide reagents for constructing either fine-scale linkage and physical maps or contig maps of cosmids or yeast artificial chromosomes.

Introduction

Human chromosome 11 contains genes responsible for several genetic diseases, including Beckwith-Wiedemann syndrome on pter→15.4 (Ping et al. 1989), familial atopy on q12→13 (Cookson et al. 1989), multiple endocrine neoplasia type 1 on q13 (Larsson et al. 1988; Nakamura et al. 1989; Bale et al. 1991), mental illness on q21 (Clair et al. 1990), ataxia telangiectasia on q22→23 (Gatti et al. 1988), tuberous sclerosis on q23 (Smith et al. 1990), and some hematopoietic diseases (Tsujimoto et al. 1985; Griffin et al. 1986). Aberrations in chromosome 11 have also been reported in some types of tumors (Scrable et al. 1987; Hopman et al. 1991). Furthermore, amplification of the region around the *hst*-1 and *int*-2 genes at q13 has been observed in several types of cancers: esophageal carcinoma (Tsuda et al. 1989), hepatocellular carcinoma (Hatada et al. 1988), breast cancer (Zhou et al. 1988), melanoma (Adelaide et al. 1988), and squamous-cell carcinoma of the head and neck (Somers et al. 1990). Deletions of constitutional material from the short arm of chromosome 11, detected, by RFLP markers, as loss of heterozygosity (LOH), have been detected in breast cancer (Theillet et al. 1986; Ali et al. 1987; Mackay et al. 1988), hepatocellular carcinoma (Wang and Rogler 1988; Fujimori et al. 1991), and bladder cancer (Fearon et al. 1985; Tsai et al. 1990). The observations cited above have implied that several tumor-suppressor genes exist on chromosome 11. Construction of a high-density map of DNA markers represents a crucial early stage in the process of identifying these genes. The map reported here will be a useful guidepost for the eventual construction of a physical map of overlapping DNA fragments (contigs) from clones of yeast artificial chromosomes (YACs) or cosmids.

Material and Methods

Construction of Genomic Library

We constructed a cosmid library from a Chinese hamster × human hybrid cell line which contained human chromosome 11 as its only human component. Four thousand clones containing human DNA inserts were identified by hybridization of colonies with la-

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beled total human DNA; this number of cosmid clones corresponded to one haploid-genome equivalent. DNA samples from 380 of these clones were prepared either by the cosmid minilysate procedure (Sambrook et al. 1989) or by means of an automated DNA preparation machine, PI-100 (Kurabo, Tokyo), and were examined for RFLPs among six unrelated individuals as described in our previous report (Tokino et al. 1991).

Somatic Hybrid Cell Lines

To map the DNA markers on chromosome 11, we used a panel of somatic hybrid cell lines which each contained a part of this human chromosome. The panels are composed of 15 cell lines: R304-A2, P3-27A, R229-3, and R28-4D, and 11 of the J1 series (J1-11, -44, -35, -8, -10, -4B, -1, -7, -9, -23, and -24) reported by Glaser et al. (1989). Chromosome 11 breakpoints in each hybrid are indicated in figure 1. These deletion panels permit division of chromosome 11 into 24 intervals (A–X on fig. 1).

Cross-Species Hybridization

To define well-conserved sequences, genomic DNAs from pig, mouse, rat, and chicken were digested with *Eco*RI and were transferred to nylon membrane after electrophoresis in an agarose gel. Hybridization with radiolabeled human chromosome 11 probes was done in 10% SDS and 7% polyethylene glycol (PEG) overnight at 65°C; the filters were then washed in 0.1 × SSC (15 mM NaCl, 1.5 mM sodium citrate) and 0.1% SDS at 50°C. Autoradiograms (KODAK XAR films) were exposed at −70°C for 2 d, with intensifying screens (Dupont Cronex Lightning Plus).

Results

Of 380 cosmid clones tested for RFLP, 123 (32.4%) revealed polymorphisms with one or more enzymes. For example, cCI11-506 (D11S589) identified polymorphisms with *Msp*I, *Taq*I, and *Bgl*II (fig. 1, arrowheads). The *Msp*I RFLP, the lower *Taq*I RFLP, and

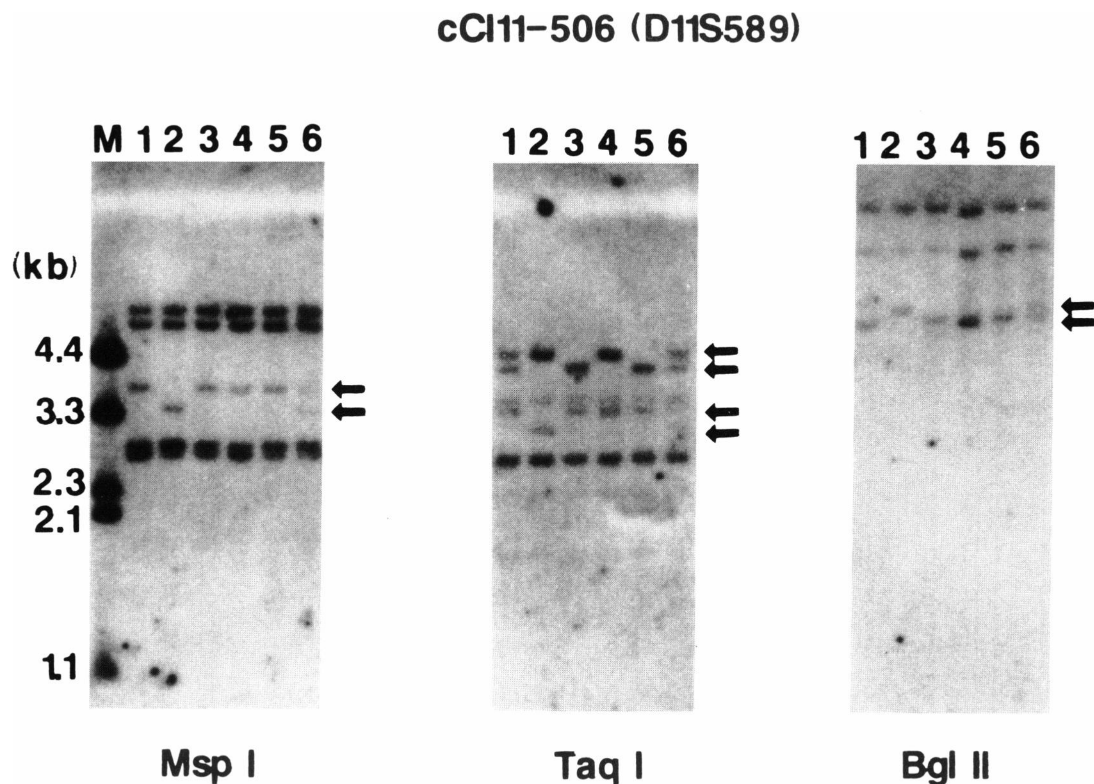

Figure 1 Autoradiogram of Southern blots hybridized with cCI11-506 (D11S589) used as a probe. Lymphoblastoid cell line DNAs derived from six unrelated Caucasians were digested with the restriction enzymes indicated. Arrowheads indicate polymorphic bands. Lane M of the *Msp*I digest contains a size marker.

Table 1

Sixty-One New RFLP Markers on Chromosome 11

Clone Name (locus symbol)	Enzyme	Allele 1 Size (kb)	Allele 1 Frequency	Allele 2 Size (kb)	Allele 2 Frequency	Location
cCI11-363 (D11S546)...	*Taq*I	5.6	.42	4.9	.58	q13.1→13.3
cCI11-368 (D11S547)...	*Rsa*I	4.1	.67	3.5	.33	q13.3→21
cCI11-374 (D11S548)...	*Taq*I	5.7	.17	3.0	.83	q23.2→23.3
cCI11-377 (D11S549)...	*Pvu*II	3.3	.17	3.2	.83	p11.2→12
cCI11-378 (D11S550)...	*Pst*I	8.0	.70	7.4	.30	p15.1
cCI11-385 (D11S551)...	*Msp*I	3.2	.33	2.2	.67	p15.5
cCI11-386 (D11S552)...	*Pvu*II	4.4	.75	4.2	.25	q21→22
cCI11-387 (D11S553)...	*Taq*I	2.9	.50	2.2	.50	q13.1→13.3
cCI11-388 (D11S554)...	*Msp*I	3.2	.25	1.6	.75	p11.2→12
cCI11-394 (D11S555)...	*Pvu*II	2.1	.67	1.5	.33	q23.2→23.3
cCI11-396 (D11S556)...	*Pst*I	7.4	.10	7.0	.90	p11.2
cCI11-400 (D11S557)...	*Msp*I	4.2	.67	3.5	.33	q13.3→21
cCI11-404 (D11S558)...	*Msp*I	4.4	.42	3.8	.58	q21→22
cCI11-410 (D11S559)...	*Pvu*II	4.4	.67	3.1	.33	q13.1→13.3
cCI11-411 (D11S560)...	*Rsa*I	3.3	.58	3.2	.42	q21→22
cCI11-414 (D11S561)...	*Taq*I	5.1	.33	3.0	.67	q21→22
cCI11-415 (D11S562)...	*Taq*I	4.4	.50	4.0	.50	q24→25
cCI11-417 (D11S563)...	*Taq*I	3.3	.75	3.2	.25	q23.2→23.3
cCI11-419 (D11S564)...	*Msp*I	4.9	.67	3.2	.33	p15.1
cCI11-422 (D11S565)...	*Bgl*II	7.5	.67	6.6	.33	p11.2→12
cCI11-425 (D11S566)...	*Msp*I	3.9	.33	2.9	.67	q21→22
cCI11-431 (D11S567)...	*Rsa*I	0.8	.70	0.7	.30	q13.3→21
cCI11-432 (D11S568)...	*Pvu*II	3.0	.40	2.8	.60	q13.3→21
cCI11-434 (D11S569)...	*Taq*I	7.9	.67	6.9	.33	p15.1
cCI11-438 (D11S570)...	*Taq*I	2.4	.25	1.7	.75	q23.2→23.3
cCI11-439 (D11S571)...	*Taq*I	5.1	.17	3.7	.83	q21→22
cCI11-440 (D11S572)...	*Pvu*II	2.3	.33	2.1	.67	p15.2→15.3
cCI11-442 (D11S573)...	*Taq*I	3.5	.50	3.2	.50	q23.2→23.3
cCI11-444 (D11S574)...	*Msp*I	3.9	.75	2.9	.25	p15.1
cCI11-445 (D11S575)...	*Bgl*II	6.3	.67	5.4	.33	q13.1→13.3
cCI11-446 (D11S576)...	*Taq*I	7.7	.33	7.2	.67	p15.5
cCI11-447 (D11S577)...	*Msp*I	4.9	.25	4.5	.75	q23.2→23.3
	*Pst*I	3.9	.60	3.8	.40	
	*Pvu*II	3.4	.25	2.9	.75	
cCI11-451 (D11S578)...	*Pvu*II	3.2	.50	2.2	.50	p11.2→12
cCI11-453 (D11S579)...	*Msp*I	5.4	.75	4.5	.25	q13.3→21
cCI11-460 (D11S580)...	*Bgl*II	4.9	.67	4.7	.33	q23.2→23.3
	*Pvu*II	2.1	.17	1.9	.83	
cCI11-465 (D11S581)...	*Msp*I	4.7	.42	4.4	.58	q23.2→23.3
	*Bgl*II	4.3	.42	3.8	.58	
cCI11-468 (D11S582)...	*Rsa*I	2.1	.33	2.0	.67	p13→14
cCI11-470 (D11S583)...	*Bgl*II	4.4	.50	3.8	.50	q21→22
cCI11-471 (D11S584)...	*Msp*I	5.0	.25	2.6	.75	q21→22
cCI11-473 (D11S585)...	*Taq*I	6.2	.50	3.1	.50	q13.1→13.3
cCI11-481 (D11S586)...	*Bgl*II	7.8	.25	7.6	.75	q21→22
	*Pst*I	4.2	.30	3.4	.70	
cCI11-484 (D11S587)...	*Pvu*II	4.5	.50	2.6	.50	p15.1
cCI11-502 (D11S588)...	*Taq*I	13.7	.75	8.4 + 5.3	.25	p15.1
	*Pvu*II	3.4	.50	2.3	.50	
cCI11-506 (D11S589)...	*Msp*I	3.7	.75	3.3	.25	q21→22
	*Taq*I	4.4	.50	4.0	.50	
	*Taq*I	3.3	.75	3.0	.25	
	*Bgl*II	5.3	.25	5.0	.75	

(*continued*)

Table 1 (continued)

Clone Name (locus symbol)	Enzyme	Allele 1 Size (kb)	Allele 1 Frequency	Allele 2 Size (kb)	Allele 2 Frequency	Location
cCI11-508 (D11S590)...	*Bgl*II	3.8	.75	3.6	.25	q21→22
cCI11-512 (D11S591)...	*Taq*I	3.3	.33	3.1	.67	q13.3→21
	*Pst*I	5.5	.30	4.7	.70	
cCI11-514 (D11S592)...	*Msp*I	5.7	.67	3.1	.33	p14→15.1
	*Taq*I	3.6	.17	3.3	.83	
cCI11-517 (D11S593)...	*Taq*I	4.6	.58	4.3	.42	q24→25
cCI11-519 (D11S594)...	*Pvu*II	3.7	.75	3.6	.25	q12→13.1
cCI11-524 (D11S595)...	*Bgl*II	4.6	.50	4.1	.50	q13.1→13.3
cCI11-529 (D11S596)...	*Taq*I	4.0	.42	3.6	.58	p14→15.1
cCI11-530 (D11S597)...	*Taq*I	5.9	.67	3.3	.33	q21→22
cCI11-539 (D11S598)...	*Rsa*I	4.2	.50	2.7	.50	q24→25
cCI11-558 (D11S599)...	*Taq*I	3.0	.83	2.6	.17	q13.1→13.3
cCI11-560 (D11S600)...	*Pst*I	7.0	.80	6.6	.20	p15.1
cCI11-565 (D11S601)...	*Msp*I	2.1	.50	1.4	.50	p15.4→15.5
cCI11-568 (D11S602)...	*Pvu*II	3.7	.25	3.3	.75	p15.1
cCI11-569 (D11S603)...	*Msp*I	4.4	.42	2.8	.58	p11.2→12
cCI11-574 (D11S604)...	*Taq*I	5.0	.42	3.3	.58	p15.1
cCI11-588 (D11S605)...	*Pst*I	4.3	.60	2.3	.40	p11.2→12
cCI11-593 (D11S606)...	*Msp*I	3.7	.50	2.2	.50	q24→25

Note.—Markers shown exclude those previously reported by Tokino et al. (1991).
[a] Estimated from typing of 6–12 unrelated individuals.
[b] Localized by hybrid cell panel.

the *Bgl*II RFLP correlate with each other, which may suggest an insertion/deletion polymorphism, and the upper *Taq*I RFLP is independent of other RFLP systems. Several clones also revealed two RFLP systems with one enzyme. Table 1 characterizes the RFLP systems that have not been reported elsewhere (Tokino et al. 1991). Thirty-five of the 123 polymorphic clones (eight in the present series) revealed RFLPs with two or more enzymes (two-system RFLP, 28; three-system RFLP, 6; four-system RFLP, 1), and four were the VNTR markers (Nakamura et al. 1987) reported elsewhere (Tokino et al. 1991). Of 162 RFLP systems present in these cosmids, more than half were detected with *Msp*I or *Taq*I. Table 2 shows the number of RFLP systems detected with each enzyme.

Figure 2 indicates the localization of 262 DNA markers, including 139 nonpolymorphic clones, into one of 24 intervals on chromosome 11, by hybridization experiments in each of the somatic hybrid cell lines. Ninety-one (44 of them were RFLP markers) were localized on the short arm; 170 clones (79 RFLPs) were on the long arm; and one was mapped to the centromeric region. No clone at region J was obtained. The DNA markers were otherwise scattered throughout chromosome 11, although some clustering was observed on R-positive bands, especially p15.1, p11.2, q13, and q23.3. In physical length, estimated cytogenetically, q13.1→13.3 and q23.3 account for approximately 15% of the total length of

Table 2

Number of Clones Revealing Polymorphism with Each Enzyme Tested[a]

Enzyme (restriction site)	No.
*Taq*I (TCGA)	49
*Msp*I (CCGG)	39
*Pvu*II (CAGCTG)	23
*Pst*I (CTGCAG)	21
*Rsa*I (GTAC)	17
*Bgl*II (AGATCT)	13
Total for all systems	162

[a] Includes all non-VNTR RFLP markers reported by Tokino et al. (1991).

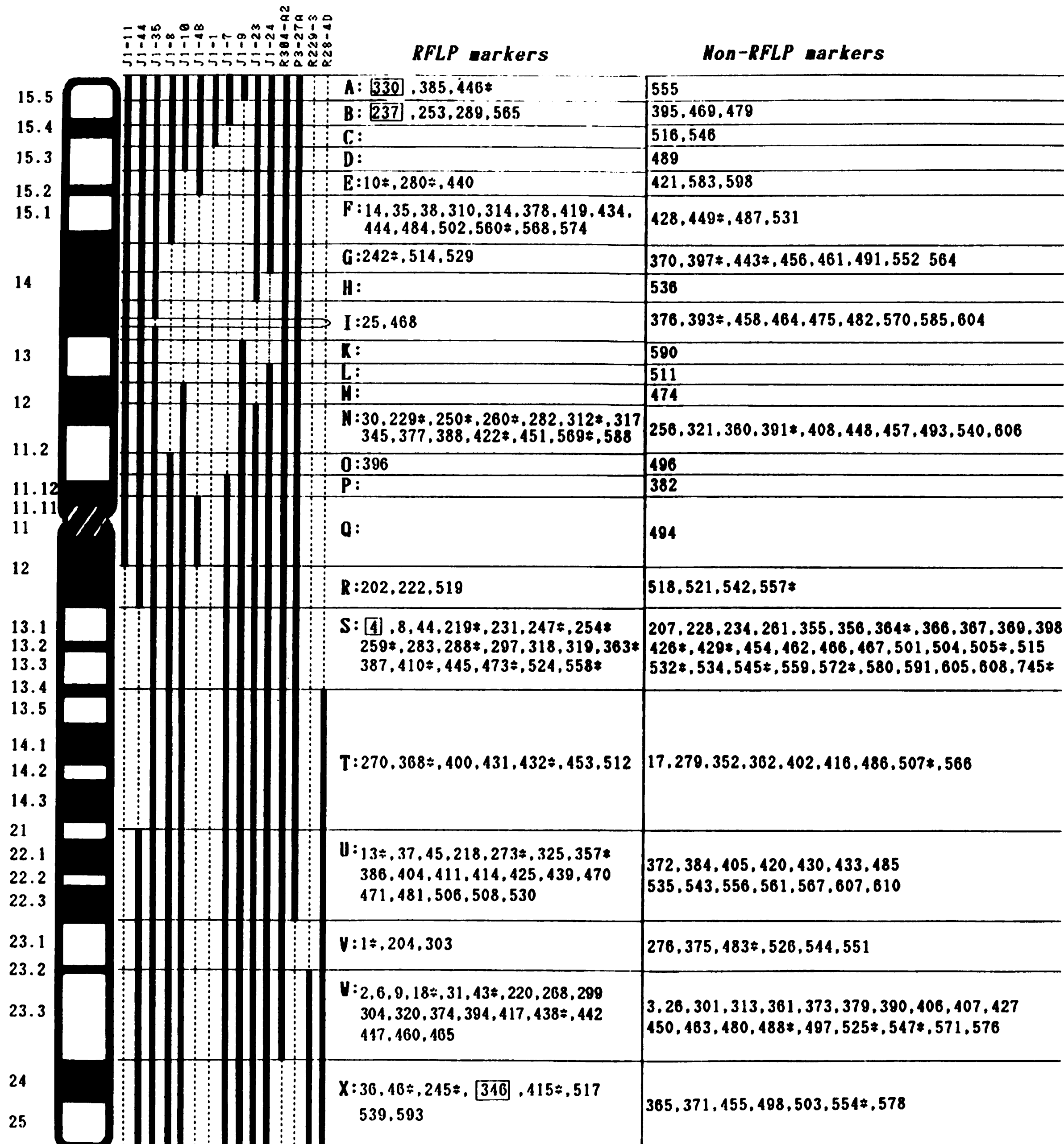

Figure 2 Mapping of 123 RFLP markers and 139 nonpolymorphic DNA markers on chromosome 11. Boldface vertical lines indicate the portion of the human chromosome that each hybrid cell line contains. Boxes indicate the four VNTR markers, and asterisks indicate clones that contain one or more sequences hybridizing to Chinese hamster DNA under stringent hybridization conditions. The hybrid cell panel divides chromosome 11 into 24 intervals, A–X. Region J, which separates region I into two subregions, is indicated by horizontal lines within the "I" segment. None of our probes hybridized in region J. (All DNA probes will be available freely through the Japanese Cancer Research Resources Bank (JCRB), 10-35, Kamiosaki 2-chome, Shinagawa, Tokyo 141, Japan.)

chromosome 11. However, more than one-third (90) of our clones were mapped to these two regions.

Several clones distinguished breakpoints in some hybrid cell lines that we had not been able to separate with the DNA markers reported previously. For example, cCI11-590 (D11S740) was mapped between two breakpoints of J1-9 and J1-24; cCI11-511 (D11S702) was between those of J1-24 and J1-10; and cCI11-396 (D11S556) and 496 (D11S694) were between those of J1-8 and J1-7.

Fifty-two (20%) of the 262 mapped clones contained DNA sequences that were conserved well in Chinese hamster. Nearly half (25) of them were localized on bands at q13.1→13.3 (region S) or q23 (regions V and W). It is interesting that 17 (one-third) of the 51 clones on q13.1→13.3 contained conserved sequences. However, only 3 of 33 clones on q21→22 (region U) showed cross-hybridization with DNA from Chinese hamster. Seventeen clones, mainly on q13, were further investigated to determine how widely they were conserved (table 3). All 17 contained sequences that were conserved in pig, mouse, and rat; two clones showed cross-hybridization with DNA from chicken, as well as with DNA from mammals, as shown in figure 3. In particular, all eight *Eco*RI fragments of cCI11-410 (D11S559) were conserved in three kinds of mammalian DNA and showed plural bands in one species.

Table 3

Conservation of Human Chromosome 11 Sequences in Four species

Clone Name (locus symbol)	Conservation of Human Chromosome 11 Sequences in[a]			
	Pig	Mouse	Rat	Chicken
cCI11-18 (D11S434)	+ + +	+ + +	+ + +	
cCI11-219 (D11S449)...	+	+	+	
cCI11-247 (D11S457)...	+ +	+ +	+ +	
cCI11-254 (D11S460)...	+ + +	+ +	+ + +	
cCI11-259 (D11S461)...		+ +	+	+ +
cCI11-288 (D11S469)...	+	+	+ +	
cCI11-363 (D11S546)...	+ +	+ + +	+ + +	
cCI11-364 (D11S633)...	+	+ +	+ +	
cCI11-410 (D11S559)...	+ + +	+ + +	+ + +	
cCI11-426 (D11S658)...	+ + +	+ + +	+ + +	
cCI11-429 (D11S661)...	+ +	+ +	+ + +	
cCI11-473 (D11S585)...	+ +	+ +	+ +	
cCI11-532 (D11S710)...	+ +	+ + +	+ + +	
cCI11-545 (D11S718)...	+ +	+ +	+ +	+
cCI11-558 (D11S599)...	+ + +	+ +	+ + +	
cCI11-572 (D11S734)...	+ +	+	+ +	
cCI11-745 (D11S749)...	+ +	+ +	+ + +	

[a] + + + = Strongly hybridized; + + = moderately hybridized; and + = weakly hybridized.

Discussion

The 123 RFLP markers on chromosome 11 that are documented here and in our previous report (Tokino et al. 1991) correspond to nearly one RFLP marker per 1-cM interval. More than half of the total of 162 RFLP systems were detected with *Msp*I or *Taq*I. Barker et al. (1984) noticed that methylated deoxycytidines at CpG frequently underwent transition to TpG. Restriction sites of both *Msp*I and *Taq*I carry one set of CpG (table 2); those of *Pvu*II and *Pst*I each contain one set of TpG and one set of CpA, which is complementary to TpG.

Several markers detected RFLPs with more than one enzyme and will be more informative. For example, cCI11-460, -502, and -514 showed 67% heterozygosity by using multiple enzymes among 12 individuals (data not shown). However, some of them, such as cCI11-506, did not increase informativeness by multiple enzymes, because of complete disequilibrium.

We have now mapped a total of 262 cosmid clones into 24 intervals, separated by somatic hybrid cell lines which contain parts of chromosome 11. These clones will be useful guideposts for construction of either a high-resolution physical map or a contig map of YACs. The density of clones in two regions (51 at q13.1→13.3 and 39 at q23.3) suggests that they are distributed every 200–300 kb; these clones ought to be valuable for analyzing these regions in particular.

The clones are relatively evenly distributed, although some clustering on R-positive bands was observed. A similar bias has been reported by others (Gardiner et al. 1990; Yamakawa et al. 1991). The reason for this bias is still unclear; it might be related to staining or to conformation of the chromosome and/or the methylation pattern of DNA. This question remains to be answered when comprehension of the human genome is complete.

To identify genomic regions containing expressed sequences is one of the important goals of the Human Genome Project. Searching well-conserved sequences in other species is an established method for obtaining essential housekeeping genes. Using that strategy, we identified 52 clones that contained conserved sequences. Nearly half of them were located on q13 and q23, where genes involved in many disorders have been mapped by linkage analysis. Isolating genes ei-

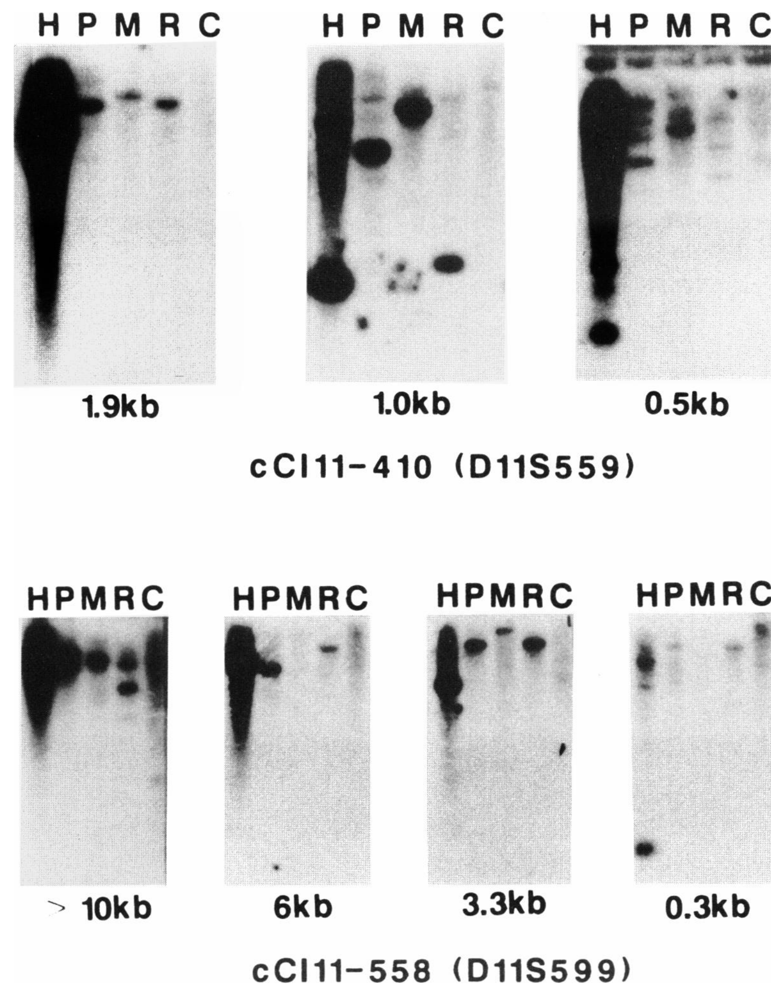

Figure 3 Conservation of chromosome 11 sequences. Cosmids cCI11-410 and -558 were digested with *Eco*RI, and each fragment was hybridized with DNA from five species: lane H, human; lane P, pig; lane M, mouse; lane R, rat; and lane C, chicken. The size of each fragment is shown at the bottom of the autoradiogram.

ther by screening cDNA libraries with these genomic cosmid clones or by means of the exon-trapping method (Duyk et al. 1990) may facilitate studies on these genetic diseases.

In addition, the RFLP markers on chromosome 11 will contribute to investigations of molecular oncology. LOH, which results in dysfunction of a tumor-suppressor gene, has been observed on the short arm of chromosome 11 in tumors of several types. The reported frequencies of LOH were 46% (6/13; Fujimori et al. 1991) and 36% (5/14; Wang et al. 1988) in hepatocellular carcinoma, 42% (5/12) in bladder carcinoma (Fearon et al. 1985), and 27% (14/51; Theillet et al. 1986) and 22% (14/65; Mackay et al. 1988) in breast cancer. A dense map containing a large number of RFLP markers will be useful both for defining the commonly deleted regions where tumor-suppressor genes exist and for detecting other aberrations in tumors.

Acknowledgments

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References

Adelaide J, Mattei MG, Marics I, Raybaud F, Planche J, Lapeyriere OD, Birnbaum D (1988) Chromosomal localization of the *hst* oncogene and its co-amplification with the *int.2* oncogene in a human melanoma. Oncogene 2: 413–416

Ali IU, Lidereau R, Theillet C, Callahan R (1987) Reduction to homozygosity of genes on chromosome 11 in human breast neoplasia. Science 238:185–188

Bale AE, Norton JA, Wong EL, Fryburg JS, Maton PN, Oldfield EH, Streeten E, et al (1991) Allelic loss on chromosome 11 in hereditary and sporadic tumors related to familial multiple endocrine neoplasia type 1. Cancer Res 51:1154–1157

Barker D, Schafer M, White R (1984) Restriction sites containing CpG show a higher frequency of polymorphism in human DNA. Cell 36:131–138

Clair DS, Blackwood D, Muir W, Carothers A, Walker M, Spowart G, Gosden C, et al (1990) Association within a family of a balanced autosomal translocation with major mental illness. Lancet 336:13–16

Cookson W, Sharp PA, Faux JA, Hopkin JM (1989) A gene for atopy (allergic asthma and rhinitis) located on 11q12–13. Cytogenet Cell Genet 51:979

Duyk GM, Kim S, Myers RM, Cox DR (1990) Exon trapping: a genetic screen to identify candidate transcribed sequences in cloned mammalian genomic DNA. Proc Natl Acad Sci USA 87:8995–8999

Fearon ER, Feinberg AP, Hamilton SH, Vogelstein B (1985) Loss of genes on the short arm of chromosome 11 in bladder cancer. Nature 318:377–380

Fujimori M, Tokino T, Hino O, Kitagawa T, Imamura T, Okamoto E, Mitsunobu M, et al (1991) Allelotype study of primary hepatocellular carcinoma. Cancer Res 51:89–93

Gardiner K, Horisberger M, Kraus J, Tantravahi U, Korenberg J, Rao V, Reddy S, et al (1990) Analysis of human chromosome 21: correlation of physical and cytogenetic maps: gene and CpG island distributions. EMBO J 9:25–34

Gatti RA, Berkel I, Boder E, Braedt G, Charmley P, Concannon P, Ersoy F, et al (1988) Localization of an ataxia-telangiectasia gene to chromosome 11q22–23. Nature 336:577–580

Glaser T, Housman D, Lewis WH, Gerhard D, Jones C (1989) A fine-structure deletion map of human chromosome 11p: analysis of J1 series hybrids. Somatic Cell Mol Genet 15:477–501

Griffin CA, McKeon C, Israel MA, Gegonne A, Ghysdael J, Stehelin D, Douglass EC, et al (1986) Comparison of constitutional and tumor-associated 11;22 translocations: nonidentical breakpoints on chromosomes 11 and 22. Proc Natl Acad Sci USA 83:6122–6126

Hatada I, Tokino T, Ochiya T, Matsubara K (1988) Co-amplification of integrated hepatitis B virus DNA and transforming gene *hst-1* in a hepatocellular carcinoma. Oncogene 3:537–540

Hopman AHN, Moesker O, Smeets AWGB, Pauwels RPE, Vooijs GP, Ramaekers FCS (1991) Numerical chromosome 1, 7, 9, and 11 aberrations in bladder cancer detected by *in situ* hybridization. Cancer Res 51:644–651

Larsson C, Skogseid B, Oeberg K, Nakamura Y, Nordenskjöld M (1988) Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. Nature 332:85–87

Mackay J, Elder PA, Porteous DJ, Steel CM, Hawkins RA, Going JJ, Chetty U (1988) Partial deletion of chromosome 11p in breast cancer correlates with size of primary tumour and oestrogen receptor level. Br J Cancer 58:710–714

Nakamura Y, Larsson C, Julier C, Byström C, Skogseid B, Wells S, Öberg K, et al (1989) Localization of the genetic defect in multiple endocrine neoplasia type 1 within a small region of chromosome 11. Am J Hum Genet 44: 751–755

Nakamura Y, Leppert M, O'Connell P, Wolff R, Holm T, Culver M, Martin C, et al (1987) Variable number of tandem repeat (VNTR) markers for human gene mapping. Science 235:1616–1622

Ping AJ, Reeve AE, Law DJ, Young MR, Boehnke M, Feinberg AP (1989) Genetic linkage of Beckwith-Wiedemann syndrome to 11p15. Am J Hum Genet 44:720–723

Sambrook J, Fritsch EF, Maniatis T (1989) Molecular cloning: a laboratory manual, 2d ed. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY

Scrable HJ, Witte DP, Lampkin BC, Cavenee WK (1987) Chromosomal localization of the human rhabdomyosarcoma locus by mitotic recombination mapping. Nature 329:645–647

Smith M, Smalley S, Cantor R, Pandolfo M, Gomez MI, Baumann R, Flodman P, et al (1990) Mapping of a gene determining tuberous sclerosis to human chromosome 11q14–11q23. Genomics 6:105–114

Somers KD, Cartwright SL, Schechter GL (1990) Amplification of the *int-2* gene in human head and neck squamous cell carcinomas. Oncogene 5:915–920

Theillet C, Lidereau R, Escot C, Hutzell P, Brunet M, Gest J, Schlom J, et al (1986) Loss of a c-H-*ras*-1 allele and aggressive human primary breast carcinomas. Cancer Res 46:4776–4781

Tokino T, Takahashi E, Mori M, Tanigami A, Glaser T, Park JW, Jones C, et al (1991) Isolation and mapping of 62 new RFLP markers on human chromosome 11. Am J Hum Genet 48:258–268

Tsai YC, Nichols PW, Hiti AL, Williams Z, Skinner DG, Jones PA (1990) Allelic losses of chromosomes 9, 11, and 17 in human bladder cancer. Cancer Res 50:44–47

Tsuda T, Tahara E, Kajiyama G, Sakamoto H, Terada M, Sugimura T (1989) High incidence of coamplification of

hst-1 and *int-2* genes in human esophageal carcinomas. Cancer Res 49:5505–5508

Tsujimoto Y, Jaffe E, Cossman J, Gorham J, Nowell PC, Croce CM (1985) Clustering of breakpoints on chromosome 11 in human B-cell neoplasms with the t(11;14) chromosome translocation. Nature 315:340–343

Wang HP, Rogler CE (1988) Deletions in human chromosome arms 11p and 13q in primary hepatocellular carcinomas. Cytogenet Cell Genet 48:72–78

Yamakawa K, Takahashi E, Saito H, Sato T, Oshimura M, Hori T, Nakamura Y (1991) Isolation and mapping of 75 new DNA markers on human chromosome 3. Genomics 9:536–543

Zhou DJ, Casey G, Cline MJ (1988) Amplification of human *int-2* in breast cancers and squamous carcinomas. Oncogene 2:279–282