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A Radiation Hybrid Map of the Distal Short Arm of Human Chromosome 11, Containing the Beckwith-Weidemann and Associated Embryonal Tumor Disease Loci

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Summary

We describe a high-resolution radiation hybrid (RH) map of the distal short arm of human chromosome 11 containing the Beckwith-Weidemann gene and the associated embryonal tumor disease loci. Thirteen human 11p15 genes and 17 new anonymous probes were mapped by a statistical analysis of the cosegregation of markers in 102 rodent-human radiation hybrids retaining fragments of human chromosome 11. The 17 anonymous probes were generated from lambda phage containing human 11p15.5 inserts, by using ALU-PCR. A comprehensive map of all 30 loci and a framework map of nine clusters of loci ordered at odds of 1,000:1 were constructed by a multipoint maximum-likelihood approach by using the computer program RHMAP. This RH map localizes one new gene to chromosome 11p15 (WEE1), provides more precise order information for several 11p15 genes (CTSD, H19, HPX, ST5, RNH, and SMPD1), confirms previous map orders for other 11p15 genes (CALCA, PTH, HBBC, TH, HRAS, and DRD4), and maps 17 new anonymous probes within the 11p15.5 region. This RH map should prove useful in better defining the positions of the Beckwith-Weidemann and associated embryonal tumor disease-gene loci.

Introduction

The distal short arm of human chromosome 11 (11p15) contains several disease-gene loci, including the Beckwith-Weidemann and associated embryonal tumor disease loci. Beckwith-Weidemann syndrome (BWS) is a genetic condition of unknown etiology with a variable clinical presentation which includes the classic triad of omphalocele, macroglossia, and gigantism. The BWS gene has previously been assigned to chromosome 11p15 by genetic linkage analysis (Koufos et al. 1989; Ping et al. 1989) and by analysis of chromosomal rearrangements involving this region of the genome (Waziri et al. 1983; Turleau et al. 1984; Journel et al. 1985; Okano et al. 1986; Weksberg et al. 1990; Mannens et al. 1991*a*, 1991*b*).

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In addition to the features noted above, patients with BWS have a predisposition to specific embryonal tumors, including Wilms nephroblastoma, adrenocortical carcinoma, hepatoblastoma, and rhabdomyosarcoma. Some of these tumors also occur sporadically in patients without BWS; both sporadic and BWS-associated tumor types exhibit loss of constitutional heterozygosity of 11p15 markers (Henry et al. 1989*b*; Reeve et al. 1989). This 11p15 region also has been implicated in breast, bladder, and pancreatic cancers; testicular tumors; and germ-line neoplasias and has been designated "multiple tumor-associated chromosome region 1."

Positional cloning of the BWS gene and other disease loci assigned to 11p15 is dependent on a high-resolution map of this region of the genome. Although a variety of mapping methods have been used by others to

order loci in the 11p15 region, including meiotic mapping (NIH/CEPH Collaborative Mapping Group 1992), in situ hybridization (Lichter et al. 1990), cosmid fingerprinting (Harrison-Lavoie et al. 1989), and somatic cell hybrid mapping panels (Glaser et al. 1989, 1990; Tanigami et al. 1992), the present map is not of sufficient resolution to allow efficient positional cloning of disease genes. In an effort to improve the resolution of the 11p15 map, we have used radiation hybrid (RH) mapping to further delineate the orders and intermarker distances of 30 11p15 loci, including known genes and new anonymous markers. RH mapping of our 17 new chromosome 11p15 probes, with respect to 13 genes from the region, improves the resolution of the 11p15 map in the vicinity of the BWS gene and should assist in the positional cloning of this disease locus.

Material and Methods

Generation of RH Cell Lines

Human-hamster RH somatic cell lines were generated according to a method described elsewhere (Cox et al. 1990; Richard et al. 1991) by using irradiated human-hamster hybrid J1 cells (containing chromosome 11 as the only human material) as the donor cell line.

Scoring of Genes in Radiation Hybrids by PCR

PCR assays were developed to determine the presence or absence of human chromosome 11 loci in radiation hybrids according to a method described elsewhere (Richard et al. 1991). Oligonucleotide sequences specific for each of the 13 gene loci were designed from published sequence (Igarashi et al. 1992; Lichy et al. 1992) or GenBank DNA sequence and are summarized in table 1. Each radiation hybrid was scored for the presence or absence of a specific human chromosome 11 marker by visual inspection of PCR-amplified DNA in ethidium-stained gels.

Generation of ALU-PCR Probes from Recombinant Bacteriophage

Genomic DNA from human-hamster hybrid J1-43a, which contains the chromosome 11 short arm distal to D11S12 as the only human material (Gerhard et al. 1987), was partially digested, size fractionated to 15–20-kb size, and cloned into bacteriophage lambda DASH vector (Stratagene). Phage containing human inserts were identified according to a method described elsewhere (Pritchard et al. 1990). ALU-PCR probes were generated from the phage by the ALU-PCR technique of Nelson et al. (1989), using either ALU primer 278 or ALU primer PDJ34 (Breukel et al. 1990). After ALU-PCR amplification and electrophoresis on agarose gels, the most intense bands were cut out and used as hybridization probes after ^{32}P labeling by the random-primer method (Feinberg and Vogelstein 1984).

Southern Blot Analysis of 11p15.5 ALU-PCR Probes on ALU-PCR–amplified RH DNA

RH genomic DNA was amplified by using either primer ALU278 or primer ALU PDJ34, electrophoresed in 1.1% GTG agarose (FMC), and transferred to Hybond N+ nylon membranes (Amersham). Membranes were prehybridized for 2–4 h at 60°C in hybridization buffer (200 mM Na_2HPO_4, 1 mM EDTA, 1% BSA, 1% SDS, and 15% formamide) and hybridized with radiolabeled probe in the same buffer at 60°C for 18–24 h. Membranes were washed at a final stringency of 0.2 × SSC, 0.1% SDS at 60–65°C for 1 h. Hybridized membranes were exposed to X-ray film at −70°C with intensifying screens for 4–72 h.

Analysis of RH Data

The order and intermarker distances of chromosome 11p15 markers were determined by a statistical analysis of the cosegregation of markers in radiation hybrids using a multipoint maximum-likelihood method. In the analysis, we assumed independent fragment retention and equal retention frequencies for all fragments (Boehnke et al. 1991). The computer program RHMAP was used with a stepwise locus-ordering approach to construct RH maps. This approach builds locus orders one locus at a time, retaining all partial locus orders with maximum likelihoods within 10^6 of the maximum likelihood of the most likely partial locus order containing the same loci. The map with the highest maximum likelihood, which contained all of the loci, was defined as the best comprehensive map. All complete locus orders with maximum likelihoods no less than one thousandth of the best locus order were tabulated. From this table, a framework map was constructed by placing loci into clusters so that all clusters could be ordered with respect to each other at odds ratios of at least 1,000:1.

Results

ALU-PCR Mapping

To obtain small-insert hybrization probes from the J1-43a phage library, we amplified phage containing

Table 1

PCR Oligonucleotide Primers and Amplification Conditions

Locus	Fragment Size (bp)	Primer Sequence	Annealing Temperature (°C)
CALCA	347	CATGCCCGAGAATGCCAACTAAACT CAGAGCAATGAGCACCGCAGCTCAG	60
CTSD	239	GTGCCCTGCCAGTCAGCGTCGTCAG CCTGCTCAGGTAGAAGGAGAAGATG	58
DRD4	414	TTCCTGTCCTGAGGGGCGGGGAG CCAGGAGCCTTCACAGCTGAGTTTG	65
H19	274	TTCCAGGCAGAAAGAGCAAGAGGGC AGACGTCCTGCTGCAACTCCCCGAG	60
HRAS	440	TCACTGACCCTCTCCCTTGACACAG TCATGCTACAGCAGCCCCTCAAAGG	65
HBBC	350	ACTGGGCATGTGGAGACAGAGAAGA TGTACCCTGTTACTTCTCCCCTTCC	65
HPX	299	GACCAGTCTCCTGGCTGCACTCAC TCCCCTCCCTTGTTTCTCACAGCCT	58
ST5	68–72	GACTGGCAGCGGGGACCTCA AGCCAAACCACTGATCTTCC	58
PTH	301	AAGCTTCTCGTGAAAACCAACCCAA CTGGGAAGAAGAGAAACAGAGAGGG	65
RNH	110	TCCCTGGACGACCGGCCTCGAGGCA TGGCAGAAATAAGCGGATCTGAGCG	65
SMPD1	212	GCCCAAATGCTGCTGTGGTTCAACC GTGTCAACTTAGGCCTCTACTCCAT	58
TH	100	CCTCCCCAGGGCGGCCCGGGGCCCA CACTTACTTACCCTTGGGGTGGGGG	56
WEE1	321	ACTGATAGAATCCAGTTTGC ATGCAATGCCTACAAAGTGC	58
ALU278		CCGAATTCGCCTCCCAAAGTGCTGGGATTACAG	55
PDJ34		GCCTCCCAAAGTGCTGGGATTACAGGCGTGAGCCA	60

NOTE.—Primer sequences used to develop locus-specific PCR assays were selected from published DNA sequences, with the exception of previously published primer sequences for HBBC (Theune et al. 1991), ALU278 (Nelson et al. 1989), and PDJ34 (Breukel et al. 1990). Abbreviations for gene loci described in this study conform to the nomenclature defined at Human Gene Mapping 11 (Junien and van Heyningen 1991): CALCA = calcitonin/calcitonin-related peptide-alpha; CTSD = cathepsin D; DRD4 = dopamine receptor D4; HRAS = Harvey ras sarcoma viral (v-Ha-ras) oncogene homologue; HBBC = hemoglobin cluster; HPX = hemopexin; INS = insulin; IGF2 = insulin-like growth factor 2; PTH = parathyroid hormone; RNH = ribonuclease/angiogenin inhibitor; SMPD1 = sphingomyelin phosphodiesterase; and TH = tyrosine hydroxylase. WEE1 is a human homologue of the yeast gene, *wee1+* (Igarashi et al. 1992), and ST5 (previously described as HTS1) is a recently cloned candidate tumor-suppressor gene (Lichy et al. 1992).

human inserts with either ALU278 or PDJ34 PCR primers (see Material and Methods). Those phage which gave intense bands on ethidium-stained agarose gels after ALU-PCR were selected for isolation of hybridization probes. Only those ALU-PCR probes which gave strong hybridization signals to ALU-PCR–amplified genomic DNA from the parent somatic cell line which contained all of human chromosome 11 (J1) were selected for scoring against radiation hybrids. Of 52 phage amplified with ALU278, 20 gave intense ethidium-stained bands which were cut out and used as hybridization probes. Ten of these ALU278 probes were positive on Southern blots of J1 DNA that had been amplified by ALU-PCR and were scored on the whole RH panel. Of 39 phage amplified with ALU PDJ34, 28 gave intense bands which were cut out and used as

hybridization probes. Nine of these PDJ34 probes were positive on Southern blots of J1 DNA that had been amplified by ALU-PCR and were scored on the whole RH panel. Seven of the PDJ34 probes defined loci different from those identified by the ALU278 probes. Thus, while many phage gave observable bands on ethidium-stained agarose gels after PCR amplification, only selected ALU-PCR probes gave intense ethidium-stained bands on agarose gels and gave reliable hybridization signals after hybridization to genomic RH DNA that was amplified with an ALU primer.

RH Map of Human 11p15 Loci

One hundred and two radiation hybrids containing chromosome 11 fragments were scored for the presence or absence of 17 11p15.5 ALU-PCR loci described above. Thirteen genes were also scored by using locus-specific sequence-tagged sites (see Material and Methods). Scorings for the anonymous probes and genes were analyzed together by using the RHMAP computer package, as described above (Boehnke et al. 1991). The locus-retention frequencies ranged from 18%–29%, with an average retention frequency of 24%. Those loci which displayed an identical pattern of retention in all hybrids tested were treated as a single locus in further analyses. We were able to distinguish 22 distinct loci by X-ray breakage (11 genes and 11 anonymous probes). We identified 402 alternative locus orders with maximum likelihoods within 1,000:1 of the most likely comprehensive RH map shown in figure 1.

To construct a framework map, markers were grouped into clusters of loci (fig. 1), labeled "A" through "I," that could be ordered with respect to each other at maximum-likelihood ratios of 1,000:1. Within each cluster, local order was also determined by using maximum-likelihood ratios. For each cluster of loci in the framework map, alternative orders with maximum likelihoods within 1,000:1 of the most likely order are given in table 2.

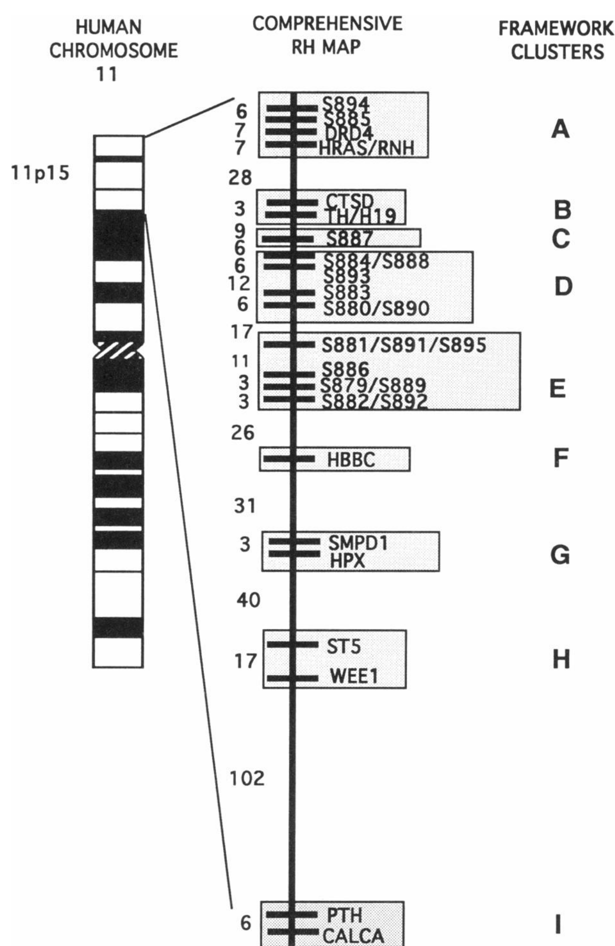

Figure 1 RH map of 11p15. Centiray distances (cR_{9000}) are shown to the left of the most likely comprehensive map. The 11p15 loci are grouped into nine shaded framework clusters labeled "A" through "I," which are ordered with respect to each other with odds of greater than 1,000:1.

Discussion

Our RH map localizes one new gene to chromosome 11 (WEE1), provides more precise order information for several 11p15 genes (SMPD1, CTSD, H19, HPX, ST5, and RNH), confirms previous map orders for the other 11p15 genes (HBBC, TH, HRAS, and DRD4), and maps 17 new anonymous probes to the 11p15.5 region (fig. 1). We map PTH close to CALCA and 3.2 times more likely to be centromeric rather than telomeric to all the other 11p15 loci. This map position is consistent with genetic linkage data (NIH/CEPH Collaborative Mapping Group 1992), fluorescence in situ hybridization, and somatic cell hybrid mapping panels, which all map PTH and CALCA centromeric to HBBC, INS, and HRAS. Mitotic deletions of some 11p15.5 markers in two different tumors suggest that CALCA is telomeric to PTH (Henry et al. 1989*a*). Proceeding toward the telomere, we map two new genes, WEE1 and ST5, distal to PTH/CALCA and proximal to the next two closely linked loci, HPX and SMPD1. The map location of ST5 is consistent with fluorescence in situ hybridization, which maps ST5 to 11p15.5 (Lichy et al. 1992), and genetic linkage data, which map ST5 centromeric to HBBC (J. H. Lichy, unpublished data). WEE1,

Table 2

Maximum-Likelihood Locus Orders within Framework Clusters

Framework Cluster and Local Order	Relative Likelihood[a]	Framework Cluster and Local Order	Relative Likelihood[a]
A:		E:	
cen-HRAS-DRD4-S885-S894-tel	1	cen-S892-S879-S886-S881-tel	1
cen-HRAS-DRD4-S894-S885-tel	4	cen-S886-S879-S892-S881-tel	1
cen-HRAS-S894-S885-DRD4-tel	6	cen-S879-S886-S892-S881-tel	6
cen-HRAS-S894-DRD4-S885-tel	6	cen-S879-S892-S886-S881-tel	6
cen-S894-S885-DRD4-HRAS-tel	44	cen-S881-S886-S879-S892-tel	13
cen-DRD4-HRAS-S894-S885-tel	391	cen-S881-S892-S879-S886-tel	13
cen-HRAS-S885-DRD4-S894-tel	802	cen-S879-S886-S881-S892-tel	18
cen-S894-HRAS-DRD4-S885-tel	805	cen-S879-S892-S881-S886-tel	18
B:		G:	
cen-TH-CTSD-tel	1	cen-HPX-SMPD1-tel	1
cen-CTSD-TH-tel	192	cen-SMPD1-HPX-tel	43
D:		H:	
cen-S880-S883-S893-S884-tel	1	cen-WEE1-ST5-tel	1
cen-S880-S883-S884-S893-tel	1	cen-ST5-WEE1-tel	51
cen-S893-S880-S883-S884-tel[b]	14		
cen-S883-S880-S893-S884-tel[b]	18	I:	
cen-S880-S893-S884-S883-tel	825	cen-CALCA-PTH-tel	1
cen-S880-S893-S883-S884-tel	855	cen-PTH-CALCA-tel	5

NOTE.—For each framework cluster of loci, alternative orders with maximum likelihoods within 1,000:1 of the most likely order are listed.

[a] The relative likelihood represents the ratio of the overall maximum likelihood of the comprehensive map to the maximum likelihood of a given local order. The likelihood of each local order was calculated by using all 22 distinguishable loci.

[b] Loci are not in the same order as that in the comprehensive map (see fig. 1). For the local order of loci in framework cluster D with relative likelihood 14, framework cluster E loci are ordered as cen-S881-S886-S879-S892-tel, rather than in their comprehensive map order. For the local order of loci in framework cluster D with relative likelihood 18, framework cluster E loci are ordered as cen-S879-S886-S881-S892-tel, rather than in the best comprehensive map order.

by virtue of its function as a mitotic inhibitor controlling the G2-to-M cell-cycle transition, and ST5, cloned by a protocol designed to identify genes associated with suppression of tumorigenecity in somatic cell hybrids of HeLa cells with fibroblasts, are both plausible candidate tumor-suppressor genes. The location of these two genes, relative to two separate 11p15.5 balanced translocations mapping centromeric to HBBC in two different BWS patients (Mannens et al. 1991*a*), deserves further study.

We more precisely localize HPX (Law et al. 1988) and SMPD1 (Pereira et al. 1991) to a region approximately 30 cR_{9000} centromeric to HBBC. We place CTSD telomeric to HBBC and close to the TH/INS/IGF2 gene cluster. H19 and TH are indistinguishable by our RH map, consistent with physical mapping data (Zemel et al. 1992) and somatic cell hybrid mapping data (Glaser et al. 1990), which places H19 near the TH/INS/IGF2 gene cluster (O'Malley and Rotwein 1988). H19 is imprinted in humans (Zhang and Tycko 1992), and several lines of evidence postulate imprinting at the BWS and associated embryonal tumor locus (Henry et al. 1989*c*, 1991; Mannens et al. 1991*a;* Brown et al. 1992). RNH and HRAS are indistinguishable by our RH map, consistent with recent localization that places RNH telomeric to IGF2 (Weremowicz et al. 1990). We map DRD4 near HRAS, consistent with recent linkage data (Gelernter et al. 1992).

Finally, in our RH map, 15 of 17 ALU probes generated from an 11p15.5 lambda phage library map between D11S12 and TH/INS/IGF2, a region implicated in BWS. This RH map is based on the assumption that those ALU-PCR markers that can be amplified in parent cell line J1 can be analyzed together with genes scored on ethidium-bromide gels by using locus-specific sequence-tagged sites. We obtained a consistent map with these assumptions, though map confirmation awaits physical mapping methods, such as pulse field-gel electrophoresis and yeast artificial chromosome contig analysis. Although the ALU-PCR probe/ALU-

PCR Southern blot method was effective in this study for mapping these 17 different probes, a drawback to this method was that only a fraction of the phage tested (17 of 52) yielded ALU-PCR bands that could be mapped reliably. These new anonymous probes generated in the 11p15.5 region should prove useful in further refining the BWS and associated embryonal tumor disease-gene region.

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