GENOMICS 35, 499–508 (1996)
ARTICLE NO. 0390

Detailed Comparative Map of Human Chromosome 19q and Related Regions of the Mouse Genome

LISA STUBBS,*,[1] ETHAN A. CARVER,*,† MARK E. SHANNON,* JOOMYEONG KIM,* JOHN GEISLER,*,† ESTELA E. GENEROSO,* BEVERLY G. STANFORD,* WILLIAM C. DUNN,* HARVEY MOHRENWEISER,‡ WOLFGANG ZIMMERMANN,§ SUZANNE M. WATT,¶ AND LINDA K. ASHWORTH‡

**Biology Division and †University of Tennessee–Oak Ridge School of Biomedical Sciences, Oak Ridge National Laboratory, P.O. Box 2009, Oak Ridge, Tennessee 37831-8077; ‡Human Genome Center, Lawrence Livermore National Laboratory, P.O. Box 808, L-452, Livermore, California 94551; §Institut for Immunobiology, University of Freiburg, Stefan-Meier-Strasse 8, D-79104 Freiburg, Germany; and ¶MRC Molecular Haemotology Unit, Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford OX3 9DU, United Kingdom*

Received December 18, 1995; accepted May 14, 1996

One of the larger contiguous blocks of mouse–human genomic homology includes the proximal portion of mouse chromosome 7 and the long arm of human chromosome 19. Previous studies have demonstrated the close relationship between the two regions, but have also indicated significant rearrangements in the relative orders of homologous mouse and human genes. Here we present the genetic locations of the homologs of 42 human chromosome 19q markers in the mouse, with an emphasis on genes also included in the human chromosome 19 physical map. Our results demonstrate that despite an overall inversion of sequences relative to the centromere, apparent "transpositions" of three gene-rich segments, and a local inversion of markers mapping near the 19q telomere, gene content, order, and spacing are remarkably well conserved throughout the lengths of these related mouse and human regions. Although most human 19q markers have remained genetically linked in mouse, one small human segment forms a separate region of homology between human chromosome 19q and mouse chromosome 17. Three of the four rearrangements of mouse versus human 19q sequences involve segments that are located directly adjacent to each other in 19q13.3–q13.4, suggesting either the coincident occurrence of these events or their common association with unstable DNA sequences. These data permit an unusually in-depth examination of this large region of mouse–human genomic homology and provide an important new tool to aid in the mapping of genes and associated phenotypes in both species.

INTRODUCTION

Genetic and physical mapping studies have now amply confirmed the notion that mouse and human chromosomes resemble each other closely within syntenic blocks that vary widely in size, containing just a few to several hundred related genes (reviewed by Copeland *et al.*, 1993). Within the best-mapped of these syntenically homologous regions, the presence and location of specific genes can be accurately predicted in one species, based upon the mapping results obtained in the other. In many cases, information regarding gene function derived from the analysis of human hereditary traits or mapped murine mutations may also be extrapolated from one species to another (e.g., Ton *et al.*, 1992; Giebel and Spritz, 1991). However, local rearrangements, including apparent deletions, inversions, insertions, and transposition events, have occurred within these homologous blocks during the course of evolution, so that relationships between syntenically homologous mouse and human regions are not always as straightforward as they may seem on the grosser level. Consequently, the power of prediction afforded in any homology region increases tremendously with the level of resolution and degree of internal consistency associated with a particular set of comparative mapping data.

One of the larger contiguous blocks of mouse–human genomic homology includes the proximal portion of mouse chromosome 7 (Mmu7), which carries all previously mapped murine homologs of human chromosome 19q (H19q) genes. Earlier studies have established the close evolutionary relationship between these two genomic regions (Saunders and Seldin, 1990; Cavanna *et al.*, 1990; Brown *et al.*, 1993; reviewed by Brilliant *et al.*, 1994), but have also indicated that a significant amount of rearrangement has occurred between the mouse and the human segments. The recent completion of detailed physical maps of human chromosome 19 (Ashworth *et al.*, 1995) provides a unique opportunity for an in-depth, point-by-point examination of the relationships between H19 and homologous regions in the mouse.

[1] To whom correspondence should be addressed. Telephone: (423) 574-0864. Fax: (423) 574-1283. E-mail: stubbsl@bioax1.bio.ornl.gov.

0888-7543/96 $18.00

In this paper, we report the genetic positions of the homologs of 42 conserved human chromosome 19q markers in the mouse, assigned primarily through the use of a single *Mus musculus* × *Mus spretus* interspecific backcross (IB) system. Mapping data presented here include numerous markers that have already been assigned to Mmu7 or H19q by previous studies and add several new markers to both the mouse genetic and the human physical maps. To permit point-by-point comparisons along the length of the homology region, we have focused mouse mapping efforts on conserved gene markers whose homologs have served as anchors in construction of the recently published H19q physical map. Our results demonstrate that gene content, order, and spacing are remarkably well conserved throughout the length of the approximately 23 cM/30 Mb region of homology between proximal Mmu7 and H19q. As suggested in earlier studies, the similarity between the two regions is interrupted by several local rearrangements in structure, including three small but significant apparent "transpositions" of gene-rich segments and a local inversion of sequences mapping near the H19q telomere. However, our data indicate that the major differences between Mmu7 and H19q are concentrated in two specific regions of the conserved linkage group and that outside these regions the two maps are essentially collinear.

Finally, these studies have identified a small interval of H19q-containing genes that define a separate linkage group located on mouse chromosome 17. Interestingly, this transposed interval is located directly adjacent to two of the three other regions of H19q that are differently arranged in the mouse genome. These results suggest either the coincident occurrence of the three rearrangement events or their common association with unstable sequences located in the human telomeric region. The detailed comparative maps produced from these data have permitted an unusually detailed, point-by-point examination of large and interesting regions of mouse–human genomic homology and provide an important new tool to aid in the assignment of new genes and mutational phenotypes in both related regions.

MATERIALS AND METHODS

Interspecific backcross mapping. To construct a genetic map of proximal Mmu7, we followed the segregation of sequences detected by mouse or human probes in the progeny of a previously described *M. musculus* × *M. spretus* interspecific backcross [(129/Rl-*p* c^{ch}/*p* c^{ch} × *M. spretus*) × 129/Rl-*p* c^{ch}/*p* c^{ch}, referred to as the 129 × Spt cross for convenience in this paper; Johnson *et al.*, 1996]. Southern blots carrying restriction digests of DNA samples prepared from each of the 160 backcross progeny were prepared and hybridized with radiolabled probes as previously described (Stubbs *et al.*, 1990), with all human markers hybridized under conditions of lower stringency (hybridized in buffer containing 45% formamide at 42°C; washed at 1× SSC at 65°C) and mouse probes hybridized at higher stringencies (hybridizations in the presence of 50% formamide; washed at 0.2× SSC at 65°C). Mapping data were stored, and map positions, with standard errors, were calculated using standard statistical methods (Silver, 1985) with the aid of the Map Manager data analysis program (Manly, 1993). Markers found not to be linked to chromosome 7 by these analyses were similarly analyzed using 160 progeny of a second IB system [(C3Hf/R1-*Mgf*$^{Sl\text{-}ENURg}$/+ × *M. spretus*) × C3Hf/R1, referred to as the C3H × Spt cross for convenience] that has been typed for numerous markers mapping to all mouse chromosomes (L. Stubbs and colleagues, unpublished results).

Human gene mapping. To localize genes within the established physical map of human chromosome 19 (Ashworth *et al.*, 1995), radiolabeled gene-specific probes were hybridized to high-density filter arrays of chromosome 19-specific cosmids (Olsen *et al.*, 1993). The cosmid clones present in this library have been analyzed using a restriction digest fingerprinting scheme (Carrano *et al.*, 1989) and assembled into contigs as reported by Branscomb *et al.* (1990). Distances between cosmid clones within these contigs were estimated using high-resolution fluorescence *in situ* hybridization (FISH) mapping methods (Brandriff *et al.*, 1991, 1994) and assigned to specific positions on the chromosome 19 metric physical map (Gordon *et al.*, 1995).

Molecular probes. All markers analyzed in this study and variant fragments used to assign them to the mouse map are described in Table 1. Several markers whose segregation in this same IB system, or whose physical linkage to markers included in this study has been reported in previously published studies, are also included in Fig. 2 for completeness. Information regarding these markers [including *Myod1, Ldha, Ldhc, Saa1, Tph,* and *Kcnc1* (Stubbs *et al.*, 1994); *Myod1* (Johnson, 1990); *Mag, Lhb, Kal1,* and *Dbp* (Stubbs *et al.*, 1996); *Xrcc1, Ckmm,* and a cluster of closely linked zinc-finger-containing genes (including genes *Zfp93* and *Zfp94*, Shannon *et al.*, 1996), and *Ccne* (Johnson *et al.*, 1996)] can be obtained from the original references. PCR-derived probes were generated with oligonucleotide primers taken from published sequences, as listed in Table 1B, from templates consisting of either mouse or human genomic DNA (100 ng/100 μl reaction) or cDNA made from total RNA of whole 16.5-d.p.c. (days postcoitum) mouse embryos. Total RNA was isolated using a modification of standard guanidinium-isothiocyanate extraction methods as described (Ausubel *et al.*, 1988). Ten micrograms of RNA was incubated with 10 units of AMV reverse transcriptase (BRL) in a 20-μl reaction for 1 h at 42°C, using buffers suggested by the manufacturer. Two microliters of this reaction was used in a single 100-μl PCR. All 100-μl PCRs were conducted using 0.2 U *Taq* polymerase or 1 U Stoffel fragment (Perkin–Elmer Cetus) in standard buffers supplied by the manufacturer, using the following program in a GeneAmp 9600 thermocycler (Perkin–Elmer/Cetus): 95°C for 4 min; (94°C for 1 min; annealing temperature for 1 min; 72°C for 2 min) × 30 cycles; 72°C for 5 min. Annealing temperatures varied from sequence to sequence and are listed in Table 1.

RESULTS

Altogether we have ordered 42 H19q markers on the mouse genetic map, including 31 that have been assigned to Mmu7 in previous studies (summarized by Brilliant *et al.*, 1994; Stubbs *et al.*, 1996; Johnson *et al.*, 1996) and 11 that had not previously been mapped in mouse. Genes mapped in mouse for the first time as part of this study include homologs of human genes encoding zinc-finger-containing proteins (ZNF42, ZNF160, ZNF134, and ZNF132) and genes encoding cytochrome oxidase 6B (*Cox6b*), the myeloid antigen *Cd33*, electron-transport flavoprotein b (*Etfb*), interleukin 11 (*Il11*), a formyl peptide receptor (*Fpr1*), a novel gene discovered through DNA sequencing of a 19q13.2 cosmid and related to a human neuroendocrine-specific protein gene, NSP (NSPL1; van de Velde *et al.*, 1994), and the mouse homolog of an expressed sequence tag

TABLE 1

Description of Probes and Variant Fragments

A. Cloned probes

Locus Name		Clone type/ species	Variant fragments			
				Size (kb)		
Human	/Mouse		Enzyme	M	S	Source/reference
PRKCG	/*Pkcc*	C/M	*Hinc*II	9.4	12	ATCC/Coussens *et al.* (1986)
IL11		C/H	*Hinc*II	6.8	2	Paul *et al.* (1990)
SYT3		C/H	*Eco*RV	16	4.3	ATCC/Adams *et al.* (1992)
CD33		C/M	*Taq*I	2	2.2	Tchilian *et al.* (1994)
ETFB		C/H	*Taq*I	4.5	3.7	Lehman and Thorpe (1991)
SNRP70		C/H	*Hinc*II	7.7	4.5	Spritz *et al.* (1987)
NGFG		C/R	*Taq*I	9	7.7	Howles *et al.* (1985)
*	/*Ngfg-rs1*	C/R	*Eco*RI	5.3	4	
*	/*Ngfg-rs2*	C/R	*Taq*I	3.5	3.2	
HRC		G/H	*Taq*I	1	1.3	ATCC/Hofmann *et al.* (1991)
LIG1		C/H	*Hinc*II	3.5	4.1	ATCC/Barnes *et al.* (1990)
STD		C/H	*Eco*RI	7	6.2	Otterness *et al.* (1992)
D19S241E	/*D7H19S241e*	C/H	*Eco*RI	4.3	2.9	ATCC/Adams *et al.* (1991)
	/*Cea5*	C/M	*Eco*RI	4.5	8.5	ATCC/Rudert *et al.* (1992)
CALM3		G/H	*Hinc*II	2.6	1.6	ATCC/Koller *et al.* (1990)
NSPL1		C/H	*Taq*I	3.4	1.8	ATCC/Adams *et al.* (1993)
CKM	/*Ckmm*	C/M	*Taq*I	6	3.2	ATCC/Nigro *et al.* (1987)
**	/*Cea2*	C/M	*Taq*I	1.3	1.5	Rudert *et al.* (1992)
**	/*Cea10*	C/M	*Hinc*II	2.4	2.8	Keck *et al.* (1995)
BGP		C/M	*Eco*RI	8	9.4	McCuaig *et al.* (1992)
IGA		C/M	*Taq*I	4.2	3	Hombach *et al.* (1988)
ATP1A3		C/H	*Hinc*II	7	5.3	ATCC/Adams *et al.* (1992)
TGFB1		C/R	*Bam*HI	4.7	1.3	ATCC/Qian *et al.* (1990)
CYP2B		C/M	*Hinc*II	4.8	4.2	Yamano *et al.* (1989)
ATP4A		C/H	*Bam*HI	11	17	Maeda *et al.* (1990)
COX6B		C/H	*Hinc*II	7	6.2	Taanman *et al.* (1989)
TCTE3		C/M	*Bam*HI	9.8	13	Rappold *et al.* (1987)
CRYA1		C/M	*Pvu*II	2.4	1.7	King *et al.* (1982)
*	/*Hba-ps4*	G/M	*BglII*	18.5	9	Fox *et al.* (1984)
FPR1		C/H	*Eco*RI	11	23	ATCC/Adams *et al.* (1992)
*	/*D17Leh180*	G/M	*Bam*HI	18.5	5.3	Bucan *et al.* (1987)

B. PCR-generated Markers

Locus human mouse	PCR parameters			Variant fragments			
					Size (kb)		
	Templ.	Primers	AT (°C)	Enzyme	M	S	Reference
ZNF42/*Zfp98*	G/M	gctggccttttctggccagat cacacgaatggtcgctcacc	55	*Taq*I	1.8	1.4	Hromas *et al.* (1991)
ZFP40/*Zfp40*	G/M	tacagttggctcagatctta tcattgcattagtaaggctt	55	*Bam*HI	8.5	9.8	Noce *et al.* (1992)
ZNF134/*Zfp134*	G/H	gttctgactatattgcacacc tctccttgtgtcaatgttc	60	*Eco*RI	3	2.4	Tommerup and Vissing (1995)
ZNF132/*Zfp132*	G/H	agctccactctcattgaaca ctcgcaaagaccacttccat	55	*Eco*RV	23	8	Tommerup and Vissing (1995)
ZNF160/*Zfp160*	G/H	ttcgttcaagcctaaccacc ctaatgacctcaccacactc	55	*Taq*I	1.8	1.6	Halford *et al.* (1994)
LIM2	G/H	atcaccatgtacagcttcatgg gttgcccaggcagtatcg	55	*Eco*RI	8.5	7	Church and Wang (1992)
RYR1	G/H	atgatccacagcaccaatggccta tagagaagctaggagttctatgag	55	*Eco*RI	13	10	Otsu *et al.* (1990)
MAG	C/H	tagcccctaccccaagaact acgttgctgagcaggagg	60	*Taq*I	6	5.2	Sato *et al.* (1989)
SCN1B	G/H	catcaccaatgtcacctaca ttgtcccccaccaggc	55	*Eco*RI	25	20	McClatchey *et al.* (1993)
PEPD/*Pep4*	G/H	atggcggcggccaccggacc ggcaatctcatctacgtact	56	*Hinc*II	8	9	Ledoux *et al.* (1994)
RRAS	C/M	cctgcacggctggacatcctggac gatggaggatgtccctgtctcctgctc	55	*Hinc*II	15	10	Lowe *et al.* (1987)
CD37	G/H	cctgagaggtaacggtc ctaggattgtggagtcgttg	55	*Bam*HI	2.9	4.1	Classon *et al.* (1989)

Note. Cloned or PCR-generated probes that were used to map the loci analyzed in this study are described in Part A or Part B of the table, respectively. Human locus name is given at left, with mouse locus names also denoted where they differ significantly. For cloned probes, the type of clone used and its species of origin are listed (H, human; M, mouse; R, rat). The sizes of variant fragments used to follow the segregation of each marker in *M. musculus* (M) or *M. spretus* (S) DNA and the restriction enzyme used to generate those fragments are also shown. References describing the probes used and source are listed at right (ATCC, American Type Culture Collection, Rockville, MD). For PCR-generated markers, PCR parameters are listed, including template used (G, genomic, C, first-strand cDNA; M, mouse and H, human DNA or RNA as source); primer sequences; and annealing temperature used to generate the product. At right the primary references for gene sequences from which oligonucleotide primers were designed are listed. Loci marker with a single asterisk in the human locus name column represent mouse loci with no known human counterparts. The double asterisks listed with mouse genes *Cea2* and *Cea10* signify that because human and mouse CEA and PSG genes have diverged considerably in both DNA and amino acid sequence, identification of specific human orthologs for any specific mouse gene, or vice versa, is difficult for these gene families. *Cea2* and *Cea10* are representative members of the mouse PSG and CEA gene families, respectively (Rudert *et al.*, 1992; Keck *et al.*, 1995).

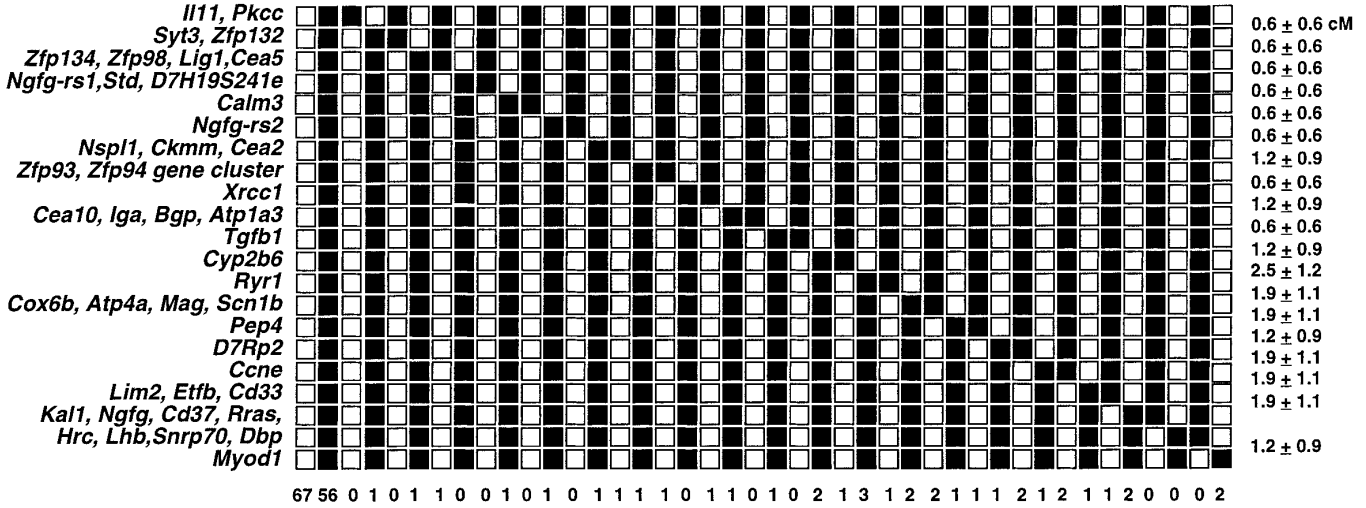

FIG. 1. Segregation patterns of markers mapping to mouse chromosome 7. Segregation patterns of the loci listed to the left of the diagram were determined in the 160 IB 129/Spt progeny, and gene order, recombination frequencies, and standard errors were calculated as described under Materials and Methods. Probes and variant fragments used to follow each locus are described in Table 1. Each column represents a type of parental or recombinant chromosome; the number of backcross animals inheriting a particular type of chromosome are listed at the bottom of the column. Black boxes represent the inheritance of a *M. spretus* allele for a particular set of loci, while white boxes denote the presence of 129/Sv alleles for the same genes. Numbers to the right between pairs of rows represent the calculated distance between a particular set of loci listed with the corresponding standard errors.

clone representing a gene with unknown function (human D19S241E; mouse *D7H19S241e*).

Results of mouse genetic mapping experiments are summarized in Fig. 1 and include some data derived from separately published work completed with the same 160 129 × Spt IB progeny used in this study (*Dbp*, *Lhb*, *Mag*, *Klk1*, *Myod1*, *Ccne*, *Xrcc1*, *Ckmm*, and the conserved zinc-finger gene cluster; see Materials and Methods). The distribution patterns obtained for those genes and their positions within the genetic map of proximal Mmu7 are included in Fig. 1 and Fig. 2 for completeness. The genetic map calculated from these data is shown aligned with the physical map of H19q in Fig. 2. The distances calculated with these IB data to lie between pairs of previously mapped mouse markers generally agree very well with intergenic distances reported by other groups (e.g., Seldin and Saunders, 1990; Cavanna *et al.*, 1990; Brown *et al.*, 1993; reviewed by Brilliant *et al.*, 1994). The relative orders of certain genes presented here differ from those presented for the same sets of genes in published consensus maps (Brilliant *et al.*, 1994), but these differences may be due primarily to errors invariably introduced in the process of combining data obtained from several different sources. Markers newly positioned within the human physical map by these studies include zinc-finger-containing genes ZNF132, ZNF134, and ZNF160 and the human homolog of the mouse gene *Zfp40*, in addition to SNRP70, LIM2, and SYT3. All other human mapping data presented in Fig. 2 are taken from the recently completed H19q physical map or other recent publications (Ashworth *et al.*, 1995; Stubbs *et al.*, 1996).

We have also located certain mouse genes that are related to human sequences that have been previously assigned to H19q by cytogenetic means, but have not been assigned unambiguously to a specific physical position using the H19 cosmid arrays (IL11 and the human homolog of *Ngfg*). In addition, we have included a murine carcinoembryonic antigen gene (*Cea5*) that has no clear homolog in human DNA and one nonconserved genomic DNA marker (*D7Rp2*), which has served as a standard marker in the construction of many published Mmu7 maps (Brilliant *et al.*, 1994). Also included in the Mmu7 map in Fig. 2 are three distinct mouse loci that were detected by a probe for the rat gene encoding the gamma subunit of nerve growth factor *Ngfg* (Howles *et al.*, 1984). The *Ngfg* gene encodes a member of the clustered kallikrein family of serine proteases, and accordingly, the rat probe used in these studies detected a number of different variant restriction fragments in most DNA digests. Most of these fragments segregated together as a group with *Klk1* near the telomeric end of the Mmu7/H19q homology region, in agreement with previously published studies (locus denoted by *Ngfg* on the mouse map; Howles *et al.*, 1984). However, two sets of *Ngfg*-related restriction fragments segregated independently of the remainder of the group in our IB system. One of the *Ngfg*-related sequences (*Ngfg-rs1*) was found to be very closely linked to *Std* and *D19S241e*, while the other (*Ngfg-rs2*) was positioned between *Calm3* and *Nspl1*. Both of these sites are located more than 15 cM proximal of the primary locus corresponding to *Ngfg* and other clustered kallikrein genes (Fig. 2). At present we cannot assess whether these related sequences represent pseudogene copies or real genes related to this multigene family.

A comparison between the mouse and the human

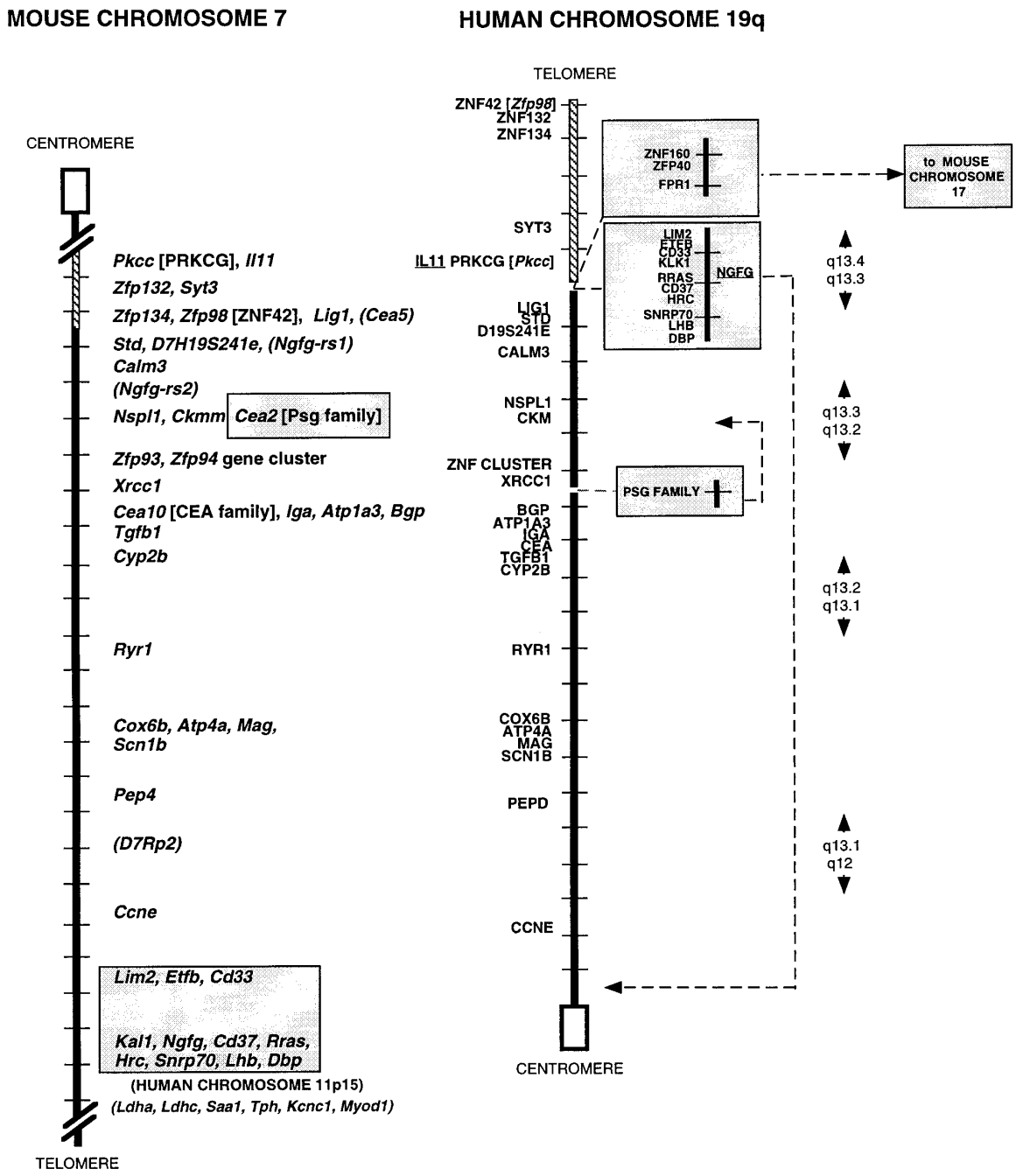

FIG. 2. Comparative map of human chromosome 19q and related regions of the mouse genome. The map on the left represents the genetic map of proximal mouse chromosome 7, as calculated from data presented in Fig. 1. Markers listed together in a single line and separated by commas gave identical segregation patterns in this IB system. Locus names presented in parentheses represent mouse genes or other markers without known human equivalents. Symbols in brackets indicate the name assigned to the homolog of the preceding mouse or human gene and are presented only where the two names differ significantly. The map on the right is extracted from the physical map of human chromosome 19 taken from Ashworth *et al.* (1995) together with data presented in this paper. Scales used are 1-cM increments in the mouse map and 1-Mb increments in the human map. The two maps are positioned to allow maximal alignment of related mouse and human markers. The hatched region on the scale of each map indicates a segment of the map that is inverted between the two species. Boxed regions indicate relative transpositions discussed in detail in the text, with a dashed arrow indicating the extent of the transposition. Gene symbols that are underlined represent sequences that have been assigned to a local region of human chromosome 19q by cytogenetic methods, but that have not yet been specifically ordered in the human physical map.

maps permits several immediate conclusions. First, as has been noted by previous authors (Saunders and Seldin, 1990), centromeric–telomeric orientation is reversed in mouse versus human DNA. The gene encoding the human protein kinase C, gamma subunit (PRKCG), is located near the telomere of 19q, while its

murine counterpart, *Pkcc*, is closely linked to the Mmu7 centromere (Fig. 2). Likewise, human cyclin E (CCNE) is located very near the centromere of 19q, while murine *Ccne* is located toward the telomeric end of the H19q homology region and situated 20 cM distal of *Pkcc* in mouse (Fig. 2; Johnson *et al.*, 1996). Aside from this overall reversal in centromeric–telomeric orientation, our data indicate that the order and relative spacing of related mouse and human genes are remarkably similar throughout the length of this large homology group, with four obvious exceptions as detailed below.

Transposition of the PSG Gene Family

The first exception to the general structural similarity between Mmu7 and H19q involves the apparent transposition of an 800-kb region containing the clustered pregnancy-specific glycoprotein (PSG) gene family (Fig. 2). This multigene family is represented in these studies by a cDNA probe encoding a murine PSG family member, *Cea2* (Rudert *et al.*, 1992). Physical mapping data have located the PSG family between the X-ray repair gene, XRCC1, and the gene encoding the β1-subunit of transforming growth factor (TGFB1) in human 19q13.2 (Olsen *et al.*, 1994). By contrast, IB mapping data place *Cea2* and several cross-hybridizing PSG sequences approximately 1.9 cM distal of *Xrcc1* in the mouse, near the *Ckmm* and *Nspl1* genes (Fig. 2). However, genes that are close neighbors of the PSG family in human 19q13.2, including members of the carcinoembryonic antigen family (CEA; represented here by the murine *Cea10* gene), BGP, IGA, and ATP1A3, are found in very similar positions in mouse and human DNA; these genes are situated between XRCC1 and TGFB1 in both species (Fig. 2). The mouse *Cea5* gene, a member of the CEA family that has no clear human homolog, maps separately of both *Cea10* and *Cea2* in the centromeric region of Mmu7 (Fig. 2).

A 4.5-Mb Cluster of Transposed Genes

The second and most obvious difference distinguishing Mmu7 and H19q involves a 4.5-Mb segment containing DBP, LHB, SNRP70, HRC, CD37, RRAS, clustered members of the kallikrein serine protease gene family (detected by the human KLK1 and rat *Ngfg* gene probes), CD33, LIM2, and ETFB. This gene-rich segment is situated between LIG1 and PRKCG near the telomere of human chromosome 19q (Ashworth *et al.*, 1995; Fig. 2). The homologs of these H19q13.3–q13.4 genes are also closely clustered in the mouse but are located more than 22 cM distal of *Lig1* and *Pkcc* and map to a region located just distal of *Ccne* (Fig. 2). The clustered genes thus appear to have been "transposed" as a group from one end of the human linkage group to the other and are most closely linked to murine sequences with counterparts that map very near the H19q centromere.

Dbp, Lhb, Snrp70, Hrc, Cd37, Rras, Ngfg, and *Klk1* are inseparable in our cross and cannot be further ordered by these methods. However, *Cd33, Etfb,* and *Lim2* do segregate from the group, allowing the entire transposed cluster to be oriented relative to the centromere of Mmu7. CD33, ETFB, and LIM2 are located near the telomeric border of the 4.5-Mb transposed human region and thus map nearest to PRKCG (Fig. 2; Ashworth *et al.*, 1995). In the mouse, *Cd33, Etfb,* and *Lim2* genes are located nearest to *Ccne* and are thus situated in a more proximal position than the rest of the genes in the transposed cluster (Fig. 2). Thus, the segment has maintained its overall proximal–distal orientation relative to other sequences in the conserved linkage group.

Taking this fact into account, and assuming that gene order within the transposed cluster is similar to that observed in the related human 4.5-Mb region, these results predict that the *Dbp* gene should be located nearest the distal border of the Mmu7/H19q homology region (Stubbs *et al.*, 1996; Fig. 2). *Dbp* is thus likely to be the nearest identified neighbor of genes of a second group of closely linked genes, including *Ldha, Ldhc, Saa1, Tph, Kcnc1,* and *Myod1,* whose human homologs are located on human 11p15 (Fig. 2; Stubbs *et al.*, 1994). Examination of the human map further allows us to predict that the proximal "breakpoint" of the 4.5-Mb transposed segment is located within the 200-kb interval separating DBP and LIG1 in human 19q13.3 (Fig. 2).

A Small Segment of H19q13.4 with Homology to Mouse Chromosome 17

Preliminary analysis with the 129 × Spt IB system indicated that the counterparts of three closely linked human 19q13.3–q13.4 genes were not linked to other 19q gene homologs in the mouse (Fig. 2). Further studies tracing the segregation of murine *Fpr1* and the homolog of human ZNF160 (*Zfp160*) in the second backcross system (C3H × Spt) demonstrated that the two genes map together in the proximal portion of mouse chromosome 17 (Fig. 3). Data obtained from these studies placed the three genes very near *D17Leh180*, a marker obtained in Mmu17 microdissection experiments and known to be located within a deletion associated with the *t* complex mutation, t^{w18} (Bucan *et al.*, 1987). These genes thus define a distinct region of homology between Mmu17 and H19q that has not been described in previous studies. In addition to the mouse homolog of ZNF160, a number of other ZNF genes are known to be clustered in the t^{w18} deletion region, including mouse gene *Zfp40* (Noce *et al.*, 1992; Crossley and Little, 1991). To confirm the relationship between this region of chromosome 17 and H19q, we mapped *Zfp40* and its homolog in both species (Figs. 2 and 3). The results confirmed the close linkage of *Zfp40, Zfp160, Fpr1,* and *D17Leh180* in the mouse (Fig. 3). When the conserved *Zfp40* probe was hybridized to the H19 cosmids, a cluster of strongly positive clones was identified

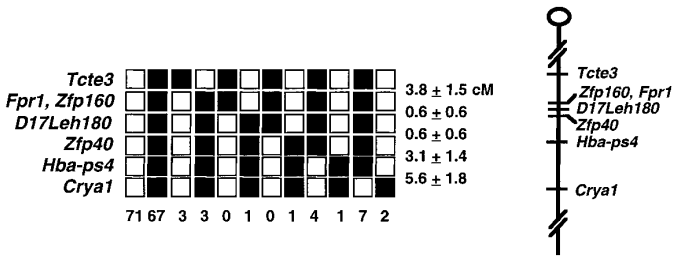

FIG. 3. Identification of a region of conserved synteny between human chromosome 19q and mouse chromosome 17. Sequences detected by human ZNF160 and FPR1 probes were found to be unlinked to other H19q homologs in the mouse and were therefore analyzed in 160 progeny of a second IB system (C3H × Spt) typed for markers derived from all mouse chromosomes. This analysis clearly showed the three genes to be tightly clustered in mouse chromosome 17. Probes and variant fragments used to follow each locus are described in Table 1. Each column represents a type of parental or recombinant chromosome; the number of backcross animals inheriting a particular type of chromosome are listed at the bottom of each column. Black boxes represent the inheritance of a *M. spretus* allele for a particular set of loci, while white boxes denote the presence of C3Hf/Rl alleles for the same genes. Numbers to the right between each pair of rows represent the calculated distance between loci represented by those rows and are listed with standard errors. On the right is a partial map of mouse chromosome 17 summarizing the positions of mouse *Zfp160*, *Zfp40*, and *Fpr1* relative to other Mmu17 genes as calculated by these data.

within a contig located between FPR1 and ZNF160, lying approximately 600 and 700 kb from contigs containing those genes, respectively (Fig. 2; this human locus has been assigned the name ZFP40 in accordance with human gene nomenclature rules). These results indicate that human counterparts of at least some members of this mouse gene cluster are located in H19q13.4, a region that is also known to be exceptionally rich in ZNF gene sequences (Ashworth *et al.*, 1995).

The approximately 2-Mb interval containing FPR1, ZNF160, and ZFP40 therefore defines a third region that is transposed in human relative to mouse DNA. The distal border of this small segment of Mmu17/H19q homology therefore lies in the 800-kb region that separates ZNF160 from PRKCG, while the proximal border is situated within the 300-kb interval between ETFB and FPR1. Since ETFB itself is located within the larger transposed segment described above, this 300-kb interval harbors breakpoints of both rearrangements (Fig. 2).

Inversion and Rearrangement of Sequences Located near the 19q Telomere

Additional differences in gene order can be observed in homologous segments located near the telomere of human 19q and the centromere of Mmu7. ZNF42 represents the most distal of all mapped H19q genes and is contained in a cosmid contig that also carries subtelomeric repeat sequences (Hoffman *et al.*, 1996). Human genes SYT3, PRKCG, and LIG1 are located 3.3, 4.4, and 10 Mb from ZNF42, respectively, in the centromeric direction, to yield the following human gene order: tel–ZNF42–SYT3–PRKCG–LIG1 (Fig. 2). In mouse, the interval bounded by *Pkcc* and the homolog of ZNF42 (which has been assigned the name *Zfp98* according to nomenclature rules) is inverted in order relative to *Lig1*, so that the genes are ordered as follows: cen–*Pkcc*–*Syt3*–*Zfp98*, *Lig1* (Fig. 2). Our results also indicate that genes located within the boundaries of this inverted segment are arranged differently in mouse and human DNA. In H19q13.4, ZNF132 lies within 0.1 Mb of ZNF42 while the related gene, ZNF134, is positioned a further 0.7 Mb away in the centromeric direction. However, in mouse *Znf134*-related sequences are located closest to *Zfp98*, while *Znf132* maps near the center of the inverted segment and is closest to *Syt3* (Fig. 2). These results indicate that the evolutionary rearrangement of this region may have involved a complicated series of events and not a simple inversion. A more detailed accounting of these events will require the application of physical mapping methods to the analysis of this ZNF gene-rich region in the mouse.

The proximal border of this inverted human interval and the distal border of the adjacent segment containing genes that have been transposed to mouse chromosome 17 are both located within the 1500-kb region between PRKCG and ZFP40 (Fig. 2). Three of the four major rearrangements that distinguish H19q from Mmu7 therefore involve adjacent segments of H19q13.3–q13.4, with breakpoints occurring in closely juxtaposed DNA sequences located within the ETFB–FPR1 and the ZNF160–PRKCG intervals.

Overall Structural Features

Aside from these four major differences, the related mouse and human genes examined in this study appear to be located in a very similar order and with remarkably similar spacing throughout the length of this 23-cM/29-Mb homology region. The relationship between recombination frequencies as calculated for Mmu7 in the 129 × Spt IB system and physical distances calculated by combined contig assembly and FISH methods in homologous regions of human chromosome 19 is roughly linear, with 1 cM in the mouse genetic map corresponding approximately to 1-Mb intervals in human 19q (Fig. 2). For example, the genetic distance between *Scn1b* and *Ccne* is calculated from these IB data to be 5 cM, while the related SCN1B–CCNE interval spans a physical distance of 4.6 Mb in human 19q12–q13.1 (Fig. 2; Ashworth *et al.*, 1995). The largest unmarked gaps present in the Mmu7 genetic map are related to human regions with a similarly low density of mapped genes. Small local exceptions to this general rule are certainly seen; for example, human CD33 and KLK1 are located within 200 kb of one another in H19q13.3, but are separated by a genetic distance of 1.9 cM (± 1.09 cM) in Mmu7. The largest discrepancies between genetic distances in mouse and human physical distances can be observed within the *Pkcc*–*Zfp98*

interval in the centromeric region of Mmu7 (Fig. 2). There is no recombination between *Syt3* and *Zfp132* in our IB system, despite the 2.5-Mb distance separating the homologs of these genes in the human map (Fig. 2). However, as mentioned above, the possibility of additional rearrangements of physical structure in this region in mouse relative to human cannot be ruled out without further study. Aside from the differences in this centromeric region, none of the other local discrepancies in human physical vs mouse genetic distances are in significant disagreement with the 99% confidence limits of the genetic calculations.

DISCUSSION

A comparison between the physical map of human chromosome 19q and the genetic map of proximal mouse chromosome 7 generated in this study demonstrates that the two regions are remarkably similar in both content and organization of related genes. The overall similarity between the two regions is disrupted by four major rearrangements large enough to be detected on the genetic level, including apparent transpositions of three blocks of genes and a relative inversion of sequences located very near the telomere of H19q. Two of the transposition events have resulted in the displacement of gene-rich segments from one position to another within the same overall linkage group, while one has resulted in the creation of a distinct and previously unrecorded region of homology between H19q and Mmu17. Other authors have presented data suggesting the existence of yet another conserved linkage group between 19q-related sequences and distal Mmu10, involving potassium channel genes *Kcnc3* and *Kcnc2* (Haas *et al.*, 1993); these genes were not included in the present study. Although KCNC2 has not been positioned within the H19 physical map, KCNC3 is located between KLK1 and RRAS and thus within the largest of the three transposed segments described in this study. If this additional conserved linkage group can indeed be verified, it should therefore span a maximum distance of 1 Mb (Ashworth *et al.*, 1995).

Using the detailed H19q physical map, we have been able to assign the borders of each rearranged segment to relatively small intervals in the human map. Interestingly, three of the four major evolutionary rearrangements involve adjacent segments of H19q13.3–q13.4; the Mmu10 homology segment proposed by Haas *et al.* (1993) would represent an additional rearrangement located within this same human region. Although the precise location of the borders of each rearranged segment will require further study, it is interesting to note that most of the evolutionary "breakpoint" regions contain tandem clusters of closely related genes. While the more proximally located transposed segment involves the pregnancy-specific glycoprotein gene family of H19q13.2, two of the three regions that define borders of the closely adjacent distal rearrangements are especially rich in tandemly clustered zinc-finger-containing genes (Ashworth *et al.*, 1995). These results invite the speculation that the large blocks of repeated DNA sequences may have contributed to the evolutionary instability of these regions within the otherwise highly conserved linkage group.

If physical distances measured between genes on H19q can be used as a guide to predict intergenic distances overall in related regions of mouse, our data would suggest a nearly 1:1 relationship between physical distance and recombination frequencies throughout the length of this 23-cM region of Mmu 7, with the possible exception of the centromerically located *Zfp98–Pkcc* interval. Interestingly, the relationship between genetic and physical distances in human chromosome 19q is very different, yielding an overall average ratio of 1 cM per 2 Mb and including several local regions with unusually high or low recombination rates (Mohrenweiser *et al.*, 1994, and unpublished data). Comparative physical mapping studies conducted in several intervals (L. Stubbs and colleagues, unpublished data) indicate that the similarities observed between the human chromosome 19q and Mmu7 on the genetic level do indeed reflect close parallels in the physical structure in related mouse and human regions.

This detailed comparative map provides a considerable new resource for predicting the presence and the precise locations of new genes and associated phenotypes throughout both chromosomal regions. The results of this study confirm that the already established physical map of H19q can be used as a guide to predict the existence of new Mmu7 genes and to estimate their physical positions relative to other conserved markers with an impressive degree of accuracy. For example, knowledge of the similarities between H19q and Mmu7 have already aided in the identification of a hitherto unknown cluster of conserved ZNF genes, including *Zfp93* and *Zfp94*, near *Xrcc1* in the mouse (Shannon *et al.*, 1996). Similar reasoning also allows us to predict with confidence that most, or perhaps all, of the numerous ZNF genes assigned to H19 are represented by similarly positioned counterparts in the mouse genome. These data provide a means of linking newly discovered H19q genes to the vast array of tools emerging to analyze gene expression and *in vivo* function in the mouse, including especially the rich and ever-expanding collections of genetically altered mutant strains.

ACKNOWLEDGMENTS

We extend our thanks to Gene Rinchik and Dabney Johnson for establishing and conducting initial analyses of the mouse IB mapping systems used in this study; Drs. Ken Gross, Richard Spritz, Yu-Chang Yang, Michael Reth, and Nicole Beauchemin for generous gifts of the *Ngfg*, SNRP70, IL11, *Iga*, and *Bgp* gene probes, respectively; Greg Lennon, Susan Tsujimoto, and Susan Hoffman for providing probes and for helpful advice during the initial stages of this work; Laurie Gordon and Anne Bergmann for high-resolution FISH mapping; Beate Fischer for assistance in analysis of the CEA and

PSG regions; and Anne Olsen and Elbert Branscomb for critical comments on the manuscript. This work was supported by grants from the U.S. DOE under Contract Nos. AC05-84OR21400 (Oak Ridge National Laboratory) and W-7405-ENG-48 (Lawrence Livermore National Laboratory), in addition to support by the Medical Research Council and Leukaemia Research Fund of Great Britain and an EU Concerted action on Haematopoietic stem cells (awarded to S.M.W.) and by the Mildred-Scheel-Stiftung für Krebsforschung (awarded to W.Z.).

REFERENCES

Adams, M. D., Soares, M. B., Kerlavage, A. R., Fields, C., and Venter, J. C. (1993). Rapid cDNA sequencing (expressed sequence tags) from a directionally cloned human infant brain cDNA library. *Nature Genet.* 4: 373–380.

Adams, M. D., Dubnick, M., Kerlavage, A. R., Moreno, R., Kelley, J. M., Utterback, T. R., Nagle, J. W., Fields, C., and Venter, J. C. (1992). Sequence identification of 2,375 human brain genes. *Nature* 355: 632–634.

Adams, M. D., Kelley, J. M., Gocayne, J. D., Dubnick, M., Polymeropoulos, M. H., Xiao, H., Merril, C. R., Wu, A., Olde, B., Moreno, R. F., Kerlavage, A. R., McCombie, W. R., and Venter, J. C. (1991). Complementary DNA sequencing: Expressed sequence tags and Human Genome Project. *Science* 252: 1651–1656.

Ashworth, L. K., Batzer, M. A., Brandriff, B., Branscomb, E., deJong, P., Garcia, E., Garnes, J., Gordon, L., Lamerdin, J. E., Lennon, G., Mohrenweiser, H., Olsen, A., Slezak, T., and Carrano, A. V. (1995). A metric physical map of human chromosome 19. *Nature Genet.* 11: 422–427.

Ausubel, F. M., Brent, R., Kingston, R. E., Moore, D. D., Seidman, J. G., Smith, J. A., and Struhl, K. (1988). "Current Protocols in Molecular Biology," Wiley, New York.

Barnes, D. E., Johnston, L. H., Kodama, K., Tomkinson, A. E., Lasko, D. D., and Lindahl, T. (1990). Human DNA ligase I cDNA: Cloning and functional expression in *Saccharomyces cerevisiae. Proc. Natl. Acad. Sci. USA* 87: 6679–6683.

Brandriff, B. F., Gordon, L. A., Fertitta, A., Olsen, A. S., Christensen, M., Ashworth, L. K., Nelson, D. O., Carrano, A. V., and Mohrenweiser, H. W. (1994). Human chromosome 19p: A fluorescence *in situ* hybridization map with genomic distance estimates for 79 intervals spanning 20 Mb. *Genomics* 23: 582–591.

Brandriff, B. F., Gordon, L. A., and Trask, B. J. (1991). A new system for high-resolution DNA sequence mapping in interphase pronuclei. *Genomics* 10: 75–82.

Branscomb, E., Slezak, T., Pae, R., Galas, D., Carrano, A. V., and Waterman, M. (1990). Optimizing restriction fragment fingerprinting methods for ordering large genomic libraries. *Genomics* 8: 351–366.

Brilliant, M. H., Williams, R. W., Conti, C. J., Angel, J. M., Oakey, R. J., and Holdener, B. C. (1994). Mouse Chromosome 7. *Mamm. Genome* 5: S104–S123.

Brown, S. D. M., Chartier, R., Johnson, K., and Cavanna, J. S. (1993). Mapping the *Hrc* gene to proximal mouse chromosome 7: Delineation of a conserved linkage group with human 19q. *Genomics* 18: 459–461.

Bucan, M., Herrmann, B. G., Frischauf, A.-M., Bautch, V. L., Bode, V., Silver, L. M., Martin, G. R., and Lehrach, H. (1987). Deletion and duplication of DNA sequences is associated with the embryonic lethal phenotype of the t^9 complementation group of the mouse *t* complex. *Genes Dev.* 1: 376–385.

Carrano, A. V., Lamerdin, J., Ashworth, L. K., Watkins, B., Branscomb, E., Slezak, T., Raff, M., de Jong, P. J., Keith, D., McBride, L., Meister, K. S., and Kronick, M. (1989). A high-resolution, fluorescence-based, semiautomated method for DNA fingerprinting. *Genomics* 4: 129–136.

Cavanna, J. S., Greenfield, A. J., Johnson, K. J., Marks, A. R., Nadal-Ginard, B., and Brown, S. D. M. (1990). Establishment of the mouse chromosome 7 region with homology to the myotonic dystrophy region of human chromosome 19q. *Genomics* 7: 12–18.

Church, R. L., and Wang, J. (1992). Assignment of the lens intrinsic membrane protein MP19 structural gene to human chromosome 19. *Curr. Eye Res.* 11: 421–424.

Classon, B. J., Williams, A. F., Willis, A. C., Seed, B., and Stamenkovic, I. (1989). The primary structure of the human leukocyte antigen CD37, a species homologue of the rat MRC OX-44 antigen. *J. Exp. Med.* 169: 1497–1502.

Copeland, N. E., Jenkins, N. A., Gilbert, D. J., Eppig, J. T., Maltais, L. J., Miller, J. C., Dietrich, W. F., Weaver, A., Lincoln, S. E., Steen, R. G., Stein, L. D., Nadeau, J. H., and Lander, E. S. (1993). A genetic linkage map of the mouse: Current applications and future prospects. *Science* 262: 57–66.

Coussens, L., Parker, P. J., Rhee, L., Yang-Feng, T. L., Chen, E., Waterfield, M. D., Francke, U., and Ullrich, A. (1986). Multiple, distinct forms of bovine and human protein kinase C suggest diversity in cellular signaling pathways. *Science* 233: 859–866.

Crossley, P. H., and Little, P. R. F. (1991). A cluster of related zinc finger protein genes is deleted in the mouse embryonic lethal mutation t^{w18}. *Proc. Natl. Acad. Sci. USA* 88: 7923–7927.

Fox, H., Silver, L. M., and Martin, G. R. (1984). An α globin pseudogene is located within the mouse *t* complex. *Immunogenetics* 19: 125–130.

Giebel, L. B., and Spritz, R. A. (1991). Mutation at the *KIT* (mast/stem cell growth factor receptor) protooncogene in human piebaldism. *Proc. Natl. Acad. Sci. USA* 88: 8696–8699.

Gordon, L. A., Bergmann, A., Christensen, M., Danganan, L., Lee, D. A., Ashworth, L. K., Nelson, D. O., Olsen, A. S., Mohrenweiser, H. W., Carrano, A. V., and Brandriff, B. F. (1995). A 30-Mb metric fluorescence *in situ* hybridization map of human chromosome 19q. *Genomics* 30: 187–194.

Haas, M., Ward, D. C., Lee, J., Roses, A. D., Clarke, V., D'Eustachio, P., Lau, P., de Meira, E. V., and Rudy, B. (1993). Localization of Shaw-related K+ channel genes on mouse and human chromosomes. *Mamm. Genome* 4: 711–715.

Halford, S., Mattei, M.-G., Daw, S., and Scambler, P. J. (1994). A novel C_2H_2 zinc-finger protein gene (ZNF160) maps to human chromosome 19q13.3–q13.4. *Genomics* 25: 322–323.

Hoffman, S. M. G., Hromas, R., Amemiya, C., and Mohrenweiser, H. W. (1996). The localization of MZF-1 at the telomere of human chromosome 19q makes it vulnerable to degeneration in aging cells. *J. Cancer Cytogenet.*, in press.

Hofmann, S. L., Topham, M., Hsieh, C.-L., and Francke, U. (1991). cDNA and genomic cloning of HRC, a human sarcoplasmic reticulum protein, and localization of the gene to human chromosome 19 and mouse chromosome 7. *Genomics* 9: 656–669.

Hombach, J., Leclercq, L., Radbruch, A., Rajewsky, K., and Reth, M. (1988). A novel 34-kd protein co-isolated with the IgM molecule in surface IgM-expressing cells. *EMBO J.* 7: 3451–3456.

Howles, P. N., Dickinson, D. P., DiCaprio, L. L., Woodworth-Gutai, M., and Gross, K. W. (1984). Use of a cDNA recombinant for the gamma subunit of murine nerve growth factor to localize members of this multigene family near the TAM-1 locus on mouse chromosome 7. *Nucleic Acids Res.* 12: 2791–2805.

Hromas, R., Collins, S. J., Hickstein, D., Raskind, W., Deaven, L., O'Hara, P., Hagen, F. S., and Kaushansky, K. (1991). A retinoic acid-responsive human zinc finger gene, MZF1, preferentially expressed in myeloid cells. *J. Biol. Chem.* 266: 14183–14187.

Johnson, D. K. (1990). "Reverse Genetics and Genes That Control Development: Initial Molecular Characterization of Two Deletion Complexes in Mouse Chromosome 7 by Random-Clone Mapping and Genetic Linkage Analysis," Doctoral Thesis, University of Tennessee, Knoxville, TN.

Johnson, D. K., Stubbs, L. J., and DeLoia, J. A. (1996). The mouse Cyclin E gene maps to chromosome 7. *Mamm. Genome* 7: 245.

Keck, U., Nedellec, P., Beauchemin, N., Thompson, J., and Zimmer-

mann, W. (1995). The Cea10 gene encodes a secreted member of the murine carcinoembryonic antigen family and is expressed in the placenta, gastrointestinal tract and bone marrow. *Eur. J. Biochem.* 229: 455–464.

King, C., Shinoharo, T., and Piatogorsky, J. (1982). Alpha-crystallin messenger RNA: More non-coding than coding sequences. *Science* 215: 985–987.

Koller, M., Schnyder, B., and Strehler, E. E. (1990). Structural organization of the human CaMIII calmodulin gene. *Biochim. Biophys. Acta* 1087: 180–189.

Ledoux, P., Scriver, C., and Hechtman, P. (1994). Four novel PEPD alleles causing prolidase deficiency. *Am. J. Hum. Genet.* 54: 1014–1021.

Lehman, T. C., and Thorpe, C. (1991). A new form of mammalian electron-transferring flavoprotein. *Arch. Biochem. Biophys.* 292: 594–599.

Lowe, D. G., Capon, D. J., Delwart, E., Sakaguchi, A. Y., Naylor, S. L., and Goeddel, D. V. (1987). Structure of the human and murine R-ras genes, novel genes closely related to ras proto-oncogenes. *Cell* 48: 137–146.

Maeda, M., Oshiman, K., Tamura, S., and Futai, M. (1990). Human gastric (H+ + K+)-ATPase gene. Similarity to (Na+ + K+)-ATPase genes in exon/intron organization but difference in control region. *J. Biol. Chem.* 265: 9027–9032.

Manly, K. F. (1993). A Macintosh program for the storage and analysis of experimental genetic mapping data. *Mamm. Genome* 4: 303–313.

McClatchey, A. I., Cannon, S. C., Slaugenhaupt, S. A., and Gusella, J. F. (1993). The cloning and expression of a sodium channel beta 1-subunit cDNA from human brain. *Hum. Mol. Genet.* 2: 745–749.

McCuaig, K., Turbide, C., and Beauchemin, N. (1992). mmCGM1a: A mouse carcinoembryonic antigen gene family member, generated by alternative splicing, functions as an adhesion molecule. *Cell Growth Differ.* 3: 165–174.

Mohrenweiser, H. W., Tsujimoto, S., Swartz, A., Gordon, L., Carrano, A. V., and Brandriff, B. (1994). Co-integration of FISH reference and genetic markers onto the physical map of human chromosome 19. *In* "Proceedings, Genomic Mapping and Sequencing, May 11–15, 1994, Cold Spring Harbor, NY," p. 174.

Nigro, J. M., Schweinfest, C. W., Rajkovic, A., Pavlovic, J., Jamal, S., Dottin, R. P., Hart, J. T., Kamarck, M. E., Rae, P. M., and Carty, M. D. (1987). cDNA cloning and mapping of the human creatine kinase M gene to 19q13. *Am. J. Hum. Genet.* 40: 115–125.

Noce, T., Fujiwara, Y., Ito, M., Takeuchi, T., Hashimoto, N., Yamanouchi, M., Higashinakagawa, T., and Fujimoto, H. (1992). A novel murine zinc finger gene mapped within the t^{w18} deletion region expresses in germ cells and embryonic nervous system. *Dev. Biol.* 155: 409–422.

Olsen, A., Combs, J., Garcia, E., Elliott, J., Amemiya, C., deJong, P., and Treadgill, G. (1993). Automated production of high density cosmid and YAC colony filters using a robotic workstation. *BioTechniques* 14: 116–123.

Olsen, A., Teglund, S., Nelson, D., Gordon, L., Copeland, A., Georgescu, A., Carrano, A., and Hammarstrom, S. (1994). Gene organization of the pregnancy-specific glycoprotein region on human chromosome 19: Assembly and anlaysis of a 700-kb cosmid contig spanning the region. *Genomics* 23: 659–668.

Otsu, K., Willard, H. F., Khanna, V. K., Zorato, F., Green, N. M., and MacLennan, D. H. (1990). Molecular cloning of cDNA encoding the Ca-2+ release channel (ryanodine receptor) of rabbit cardiac muscle sarcoplasmic reticulum. *J. Biol. Chem.* 265: 13472–13483.

Otterness, D. M., Wieben, E. D., Wood, T. C., Watson, W. G., Madden, B. J., McCormick, D. J., and Weinshilboum, R. M. (1991). Human liver dehydroepiandrosterone sulfotransferase: Molecular cloning and expression of cDNA. *Mol. Pharmacol.* 41: 865–872.

Paul, S. R., Bennett, F., Calvetti, J. A., Kelleher, K., Wood, C. R., O'Hara, R. M., Jr., Leary, A. C., Sibley, B., Clark, S. C., Williams, D. A., and Yang, Y.-C. (1990). Molecular cloning of a cDNA encoding interleukin 11, a stromal cell-derived lymphopoietic and hematopoietic cytokine. *Proc. Natl. Acad. Sci. USA* 87: 7512–7516.

Qian, S. W., Kondaiah, P., Roberts, A. B., and Sporn, M. B. (1990). cDNA cloning by PCR of rat transforming growth factor beta-1. *Nucleic Acids Res.* 18: 3059.

Rappold, G., Stubbs, L., Labeit, S., Crkvenjakov, R. B., and Lehrach, H. (1987). Identification of a testis-specific gene from the mouse *t*-complex next to a CpG island. *EMBO J.* 6: 1975–1980.

Rudert, F., Saunders, A. M., Rebstock, S., Thompson, J. A., and Zimmermann, W. (1992). Characterization of murine carcinoembryonic antigen gene family members. *Mamm. Genome* 3: 262–273.

Sato, S., Fujita, N., Kurihara, T., Kuwano, R., Sakimura, K., Takahashi, Y., and Miyatake, T. (1989). cDNA cloning and amino acid sequence for human myelin-associated glycoprotein. *Biochem. Biophys. Res. Commun.* 163: 1473–1480.

Saunders, A. M., and Seldin, M. F. (1990). A molecular genetic linkage map of mouse chromosome 7. *Genomics* 8: 525–535.

Shannon, M., Ashworth, L. K., Mucenski, M. L., Lamerdin, J. E., Branscomb, E., and Stubbs, L. (1996). Comparative analysis of a conserved zinc-finger gene cluster on human chromosome 19q and mouse chromosome 7. *Genomics* 33: 112–120.

Silver, J. (1985). Confidence limits for estimates of gene linkage analysis of recombinant inbred strains. *J. Hered.* 76: 436–440.

Spritz, R. A., Strunk, K., Surowy, C. S., Hoch, S. O., Barton, D. E., and Francke, U. (1987). Human U1-70K snRNP protein: cDNA cloning, chromosomal localization, expression, alternative splicing and RNA-binding. *Nucleic Acids Res.* 15: 10373–10391.

Stubbs, L., Carver, E., Ashworth, L., and Lopez-Molina, L. (1996). Location of the DBP transcription factor gene in man and mouse. *Mamm. Genome* 7: 65–67.

Stubbs, L. J., Rinchik, E. M., Goldberg, E., Rudy, B., Handel, M. A., and Johnson, D. K. (1994). The homologs of six human chromosome 11p15 genes are clustered within a 500-kb region of proximal mouse chromosome 7. *Genomics* 24: 324–332.

Stubbs, L., Huxley, C., Hogan, B., Evans, T., Fried, M., Duboule, D., and Lehrach, H. (1990). The HOX-5 and surfeit gene clusters are linked in the proximal portion of mouse chromosome 2. *Genomics* 6: 645–650.

Taanman, J. W., Schrage, C., Ponne, N., Bolhuis, P., de Vries, H., and Agsteribbe, E. (1989). Nucleotide sequence of cDNA encoding subunit VIb of human cytochrome c oxidase. *Nucleic Acids Res.* 17: 1766.

Tchilian, E. Z., Beverley, P. C. L., Young, B. D., and Watt, S. M. (1994). Molecular cloning of two isoforms of the murine homolog of the myeloid CD33 antigen. *Blood* 83: 3188–3198.

Tommerup, N., and Vissing, H. (1995). Isolation and fine mapping of 16 novel human zinc finger-encoding cDNAs identify putative candidate genes for developmental and malignant disorders. *Genomics* 27: 259–264.

Ton, C. T., Miwa, H., and Saunders, G. F. (1992). *Small eye (Sey):* Cloning and characterization of the murine homolog of the human Aniridia gene. *Genomics* 13: 251–256.

van de Velde, H. J. K., Roebroek, A. J. M., Senden, N. H. M., Ramaekers, F. C. S., and Van de Ven, W. J. M. (1994). *NSP*-encoded reticulons, neuroendocrine proteins of a novel gene family associated with membranes of the endoplasmic reticulum. *J. Cell Sci.* 107: 2403–2416.

Yamano, S., Nhamburo, P. T., Aoyama, T., Meyer, U. A., Inaba, T., Kalow, W., Gelboin, H. V., McBride, O. W., and Gonzalez, F. J. (1989). cDNA cloning and sequence and cDNA-directed expression of human P450IIB1: Identification of a normal and two variant cDNAs derived from the CYP2B locus on chromosome 19 and differential expression of the IIB mRNAs in human liver. *Biochemistry* 28: 7340–7348.