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A Genetic Linkage Map of Mouse Chromosome *10*: Localization of Eighteen Molecular Markers Using a Single Interspecific Backcross

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ABSTRACT

Interspecific mouse backcross analysis was used to generate a molecular genetic linkage map of mouse chromosome *10*. The map locations of the *Act-2*, *Ahi-1*, *Bcr*, *Braf*, *Cdc-2a*, *Col6a-1*, *Col6a-2*, *Cos-1*, *Esr*, *Fyn*, *Gli*, *Ifg*, *Igf-1*, *Myb*, *Pah*, *pg^{cha}*, *Ros-1* and *S100b* loci were determined. These loci extend over 80% of the genetic length of the chromosome, providing molecular access to many regions of chromosome *10* for the first time. The locations of the genes mapped in this study extend the known regions of synteny between mouse chromosome *10* and human chromosomes *6*, *10*, *12* and *21*, and reveal a novel homology segment between mouse chromosome *10* and human chromosome *22*. Several loci may lie close to, or correspond to, known mutations. Preferential transmission of *Mus spretus*-derived alleles was observed for loci mapping to the central region of mouse chromosome *10*.

THE development of mouse molecular genetic linkage maps has proved invaluable for the structural and functional characterization of the mouse genome. First, molecular genetic linkage maps have identified molecular markers that represent previously isolated mouse mutations (CHABOT *et al.* 1988; GEISSLER, RYAN and HOUSMAN 1988; BALLING, DEUTCH and GRUSS 1988). Second, molecular genetic linkage maps have been utilized to determine whether newly identified genes or viral integration sites are homologous to known genes or mutations (BUCHBERG *et al.* 1988; MUCENSKI *et al.* 1988; SOLA *et al.* 1988; BARTHOLOMEW *et al.* 1988). Third, molecular genetic linkage maps have been used for comparative mapping between mouse and human (or other) genomes [reviewed by NADEAU (1989) and SEARLE *et al.* (1989)]. Comparative mapping can ultimately lead to the identification of mouse models of human diseases (BRUETON *et al.* 1988; WINTER 1988; RYDER-COOK *et al.* 1988; GLASER and HOUSMAN 1989).

One of the most powerful methods for mapping a large number of molecular markers in the mouse is interspecific backcrosses (IBs) between distantly related species of mice [reviewed by GUENET (1986) and AVNER *et al.* (1988)]. The evolutionary divergence between species has resulted in an accumulation of DNA sequence differences (BONHOMME *et al.* 1984) that facilitates the detection of restriction fragment length polymorphisms (RFLPs) required for mapping molecular markers (FERRIS, SAGE and WILSON 1982; ROBERT *et al.* 1985) [reviewed by GUENET (1986) and AVNER *et al.* (1988)]. In a laboratory setting, the wild mouse species *Mus spretus* will interbreed with inbred laboratory mouse strains to produce fertile F_1 females and sterile F_1 males (BONHOMME *et al.* 1984). The F_1 females can then be backcrossed to generate the N_2 progeny used in mapping studies.

An IB involving the inbred laboratory mouse strain C57BL/6J and *M. spretus* was used to create a multilocus molecular genetic linkage map of mouse chromosome *10*. Mutations previously mapped to mouse chromosome *10* include many loci affecting coat color, hematopoiesis, neural development, behavior, bone development and growth (summarized by GREEN 1989). We were interested in creating a molecular genetic map of chromosome *10* to localize proto-oncogenes, common sites of viral integration, growth factors, growth factor receptors and other genes affecting cell differentiation and growth. Prior to this study, only three molecular markers had been positioned on chromosome *10*. The *Myb* proto-oncogene had been mapped to chromosome *10* by *in situ* hybridization and mapped relative to *Steel* (*Sl*) in intraspecific crosses (SAKAGUCHI *et al.* 1984; TAYLOR and ROWE 1989). *Phenylalanine hydroxylase* (*Pah*) had been mapped to chromosome *10* by IBs and by *in situ* hybridization analysis (BODE *et al.* 1988; LEDLEY *et al.* 1988). The *autosomal Zinc finger protein* (*Zfa*) had been mapped relative to *Myb* and *Pah* in IBs (MITCHELL *et al.* 1989). Several other loci had been placed on chromosome *10* by somatic cell hybrid analysis, including *Abelson helper virus integration site-1* (*Ahi-1*),

collagen α1(VI) (*Col6a-1*), collagen α2(VI) (*Col6a-2*), interferon-γ (*Ifg*), and *S100 protein, β subunit* (*S100b*) (POIRIER, KOZAK and JOLICOEUR 1988; WEIL *et al.* 1988; NAYLOR, GRAY and LALLEY 1984). In addition, an anonymous mouse probe identifying the *Cos-1* locus had been placed on chromosome *10* by *in situ* hybridization (G. RADICE, J. LEE and F. COSTANTINI, personal communication). All of these molecular markers except *Zfa* were mapped in our IB relative to each other and formed the core of reference loci used to localize previously unmapped genes. After the reference loci were placed on mouse chromosome *10* using a single [(C57BL/6J × *M. spretus*)F_1 × C57BL/6J] IB, an *actin-related* locus (*Act-2*), the *breakpoint cluster region* gene (*Bcr*), the *Braf transforming* gene (*Braf*), a *cell division cycle control protein* gene (*Cdc-2a*), the *estrogen receptor* (*Esr*), the *Fyn proto-oncogene* (*Fyn*), the *glioblastoma proto-oncogene* (*Gli*), the *insulin-like growth factor-1* gene (*Igf-1*), a transgenic integration at the *pygmy* locus (pg^{cha}), and the *Ros-1 proto-oncogene* (*Ros-1*) were mapped to chromosome *10*.

The results of the IB analysis provide an unambiguous orientation of 18 molecular markers that span most of mouse chromosome *10*. The map locations of the loci compared with the composite genetic linkage map suggests that several probes may lie close to, or correspond to, known mouse mutations. The results also reveal extensive regions of synteny with human chromosomes *6*, *10*, *12* and *21*, and reveal a novel homology segment with human chromosome *22*.

MATERIALS AND METHODS

Mice: The interspecific backcross [(C57BL/6J × *M. spretus*)F_1 × C57BL/6J] was performed at the NCI-Frederick Cancer Research Facility as described by BUCHBERG *et al.* (1988, 1989).

Probes: The probe for the *Abelson helper virus integration site-1* (*Ahi-1*) was a mouse *Pst*I-*Hin*dIII genomic fragment cloned in pUC18 (p2–1; POIRIER, KOZAK and JOLICOEUR 1988) that was a gift from P. JOLICOEUR [Clinical Research Institute of Montreal (Montreal, Quebec, Canada)].

The probe for the *actin*-related locus (*Act-2*) was a chicken *β-actin* full-length cDNA cloned in pBR322 (β2000; CLEVELAND *et al.* 1980) that was a gift from S. H. HUGHES [NCI-Frederick Cancer Research Facility (Frederick, Maryland)].

The probes for the *breakpoint cluster region gene* (*Bcr*) were: 1) a mouse cDNA *Eco*RI fragment cloned in pT218 (A. DEKLEIN, unpublished results) that was a gift from A. DEKLEIN [NCI-Frederick Cancer Research Facility (Frederick, Maryland)]; 2) a mouse genomic 1.8-kilobase (kb) *Eco*RI/*Hin*dIII fragment cloned in pBluescript SK+ that is homologous to the human *BCR* exon 1 (2–21; N. HEISTERKAMP and J. GROFFEN, unpublished results); and 3) a human cDNA *Xho*I/*Bgl*II fragment from exon 1 of the *BCR* gene (probe 1; HEISTERKAMP, KNOPPEL and GROFFEN 1988).

The probe for the *Braf transforming* gene (*Braf*) was a human cDNA *Eco*RI-*Xho*I fragment cloned in pUC25 (pEX; IKAWA *et al.* 1988) that was a gift from T. YAMAMOTO [University of Tokyo (Tokyo, Japan)].

The probe for the *cell division cycle control protein* gene (*Cdc-2a*) was a mouse cDNA *Eco*RI fragment cloned in pBluescript SK+ (C1-BS; CISEK and CORDEN 1989) that was a gift from J. L. CORDEN [Johns Hopkins School of Medicine (Baltimore, Maryland)].

The probes for *collagen α1(VI)* (*Col6a-1*) (p18; WEIL *et al.* 1988) and *collagen α2(VI)* (*Col6a-2*) (p1; CHU *et al.* 1987) were human cDNA *Eco*RI fragments cloned in pUC19; both probes were gifts from M.-L. CHU [Thomas Jefferson University (Philadelphia, Pennsylvania)].

The anonymous mouse probe (*Cos-1*) was a gel-purified mouse brain cDNA 1.2-kb *Eco*RI fragment (p2351; G. RADICE, J. LEE and F. COSTANTINI, unpublished results) that was a gift from F. COSTANTINI [Columbia University, College of Physicians and Surgeons (New York, New York)].

The probe for the *estrogen receptor* (*Esr*) was a human cDNA *Eco*RI fragment cloned in pBR322 (pOR3; GREEN *et al.* 1986) that was purchased from the American Type Culture Collection (Rockville, Maryland).

The probe for the *Fyn proto-oncogene* (*Fyn*) was a human cDNA *Sac*I fragment cloned in pUC18 (KAWAKAMI, PENNINGTON and ROBBINS 1986) that was a gift from K. ROBBINS [National Institutes of Health (Bethesda, Maryland)].

The probe for the *glioblastoma proto-oncogene* (*Gli*) was a mouse genomic *Eco*RI/*Hin*dIII fragment cloned into pBluescript (pMGLI-RS; K. W. KINZLER, J. M. RUPPERT and B. VOGELSTEIN, unpublished results; KINZLER *et al.* 1988) that was a gift from B. VOGELSTEIN [The Johns Hopkins Oncology Center (Baltimore, Maryland)].

The probe for *interferon-γ* (*Ifg*) was a mouse cDNA *Bam*HI fragment cloned in pCD (K.-I. ARAI, unpublished results) that was a gift from H. YOUNG [NCI-Frederick Cancer Research Facility (Frederick, Maryland)] with permission from K.-I. ARAI [DNAX (Palo Alto, California)].

The probe for the *insulin-like growth factor-1* gene (*Igf-1*) was a mouse cDNA *Eco*RI fragment cloned in pBR327 (pmigf1–2; BELL *et al.* 1985) that was a gift from G. BELL [Howard Hughes Medical Institute (Chicago, Illinois)].

The probe for the *Myb proto-oncogene* (*Myb*) was a mouse genomic *Xba*I fragment cloned in pUC12 (SHEN-ONG *et al.* 1984) that was a gift from G. SHEN-ONG [National Cancer Institute (Bethesda, Maryland)].

The probe for *phenylalanine hydroxylase* (*Pah*) was synthesized by the polymerase chain reaction amplification (SAIKI *et al.* 1988) of mouse liver cDNA using synthetic oligodeoxynucleotides corresponding to nucleotides 474–493 and the complement of nucleotides 1254–1273 of the rat phenylalanine hydroxylase cDNA sequence (DAHL and MERCER 1986).

The probe for the transgenic integration at the *pygmy* locus (pg^{cha}) was a mouse genomic fragment cloned in pBluescript (XIANG, BENSON and CHADA 1990).

The probe for the *Ros-1 proto-oncogene* (*Ros-1*) was a human cDNA *Sal*I fragment cloned in pAT (pSc3.2/23; BIRCHMEIER *et al.* 1986) that was a gift from C. BIRCHMEIER [Cold Spring Harbor Laboratory (Cold Spring Harbor, New York)].

The probe for the *S100 protein, β subunit* gene (*S100b*) was a human genomic *Eco*RI-*Hin*dIII fragment cloned in pBluescript KS+ (pHS 100/2.2; ALLORE *et al.* 1988) that was a gift from R. DUNN [University of Toronto (Toronto, Canada)].

DNA isolation and Southern blot analysis: High molecular weight genomic DNAs were prepared from frozen mouse tissues as described (JENKINS *et al.* 1982). Restriction endonuclease digestions, agarose gel electrophoresis, Southern transfers and hybridizations were also performed as described (JENKINS *et al.* 1982), except that Zetabind membrane (CUNO, Inc.) was used for Southern transfers. The human S100 protein, β-subunit probe was hybridized using

a low stringency procedure (MANIATIS, FRITSCH and SAMBROOK 1982) as modified by JUSTICE *et al.* (1990).

Probes were labeled with [α-^{32}P]dCTP (Amersham) using a nick translation kit (Amersham) for whole plasmids or a multiprime DNA labeling kit (Amersham) for gel-purified fragments. Southern blot filters hybridized with ^{32}P-labeled probes were routinely washed three times in 0.5 × SSCP, 0.1% SDS for 30 min/wash at 65° with the following exceptions. Southern blot filters hybridized with the *Bcr*, *Braf*, *β-Actin*, and *Esr* probes were washed three times in 1 × SSCP, 0.1% SDS, 30 min/wash at 65°. Southern blot filters hybridized with the *S100b* probe were washed to a final stringency of 0.2 × SSCP at 42°. Probes were removed from Southern filters as described by JUSTICE *et al.* (1990).

Statistical analysis: Standard errors of the recombination frequencies from the results of the IB study were determined as described by GREEN (1981), using the computer program SPRETUS MADNESS [developed by D. DAVE (Data Management Services, Inc.) and A. M. BUCHBERG (ABL-Basic Research Program) NCI-Frederick Cancer Research Facility]. Gene order was determined by minimizing the number of multiple crossovers along the length of the chromosome ("pedigree analysis"; reviewed by AVNER *et al.* 1988), and confirmed by the maximum likelihood analysis (D. T. BISHOP, 1985). Statistical analysis of transmission ratio distortion was carried out using a G test on partitioned samples (SOKAL and ROHLF 1981).

RESULTS

Eighteen loci were mapped using Southern analysis of DNAs from N_2 progeny of a [(C57BL/6J × *M. spretus*)F_1 × C57BL/6J] backcross. C57BL/6J and *M. spretus* DNAs were digested with several restriction enzymes and analyzed by Southern hybridization with each of the probes listed in Table 1. At least one informative RFLP was identified for each probe. The segregation of the *M. spretus* allele(s) detected by each probe was followed in the N_2 progeny by Southern analysis. Each backcross animal appeared to be either homozygous for the C57BL/6J allele or heterozygous for the *M. spretus* and C57BL/6J alleles at each locus. The order of the 18 loci [(*Act-2*, *Esr*), (*Myb*, *Ahi-1*), *Braf*, *Fyn*, *Ros-1*, *Cos-1*, *Cdc-2a*, *Bcr*, (*Col6a-1*, *Col6a-2*, *S100b*), *Pah*, *Igf-1*, *Ifg*, *pg^{cha}* and *Gli*] was determined by the analysis of 108 N_2 progeny (Figure 1). Note that the *S100b* locus was typed for a subset of the N_2 progeny shown in Figure 1; no crossovers were observed between the *S100b* and *Col6a-1*/*Col6a-2* loci in 97 N_2 progeny, giving an upper 95% confidence limit of 3.0 centiMorgans (cM) between *S100b* and *Col6a-1*/*Col6a-2*. Additional N_2 progeny were analyzed in a pairwise combination for the *Ahi-1* and *Myb* loci; no crossovers were detected between the *Ahi-1* and *Myb* loci in 169 N_2 progeny, giving an upper 95% confidence limit of 1.7 cM between *Ahi-1* and *Myb*. Additional N_2 progeny were also analyzed for the *Esr* and *Act-2* loci; 3 crossovers were detected in a total of 179 N_2 progeny. Using *Myb* as a third marker, these crossovers placed *Act-2* 1.7 ± 1.0 cM proximal of *Esr*.

The ratios of the total number of mice carrying recombinant chromosomes to the total number of mice analyzed for each pair of loci and the determined gene order are centromere–*Act-2*–3/179–*Esr*–5/108–(*Myb*–0/169–*Ahi-1*)–6/108–*Braf*–1/108–*Fyn*–6/108–*Ros-1*–4/108–*Cos-1*–5/108–*Cdc-2a*–1/108–*Bcr*–1/108–(*Col6a-1*–0/108–*Col6a-2*–0/97–*S100b*)–8/108–*Pah*–1/108–*Igf-1*–26/108–*Ifg-1*–1/108–*pg^{cha}*–1/108–*Gli*. The map distance ± the standard error (in cM) between each pair of loci is centromere–*Act-2* –1.7 ± 1.0–*Esr*–4.6 ± 2.0–[*Myb*, *Ahi-1*]–5.6 ± 2.2–*Braf*–0.9 ± 0.9–*Fyn*–5.6 ± 2.2–*Ros-1*–3.7 ± 1.8–*Cos-1*–4.6 ± 2.0–*Cdc-2a*–0.9 ± 0.9–*Bcr*–0.9 ± 0.9–[*Col6a-1*, *Col6a-2*, (*S100b*)]–7.4 ± 2.5–*Pah*–0.9 ± 0.9–*Igf-1*–24.1 ± 4.1–*Ifg*–0.9 ± 0.9–*pg^{cha}*–0.9 ± 0.9–*Gli*.

The *Bcr* locus was mapped initially using a mouse cDNA probe corresponding to the 3′ end of the human *BCR* gene (A. DEKLEIN, unpublished results). In humans, probes corresponding to the 3′ end of the *BCR* gene detect four distinct loci on chromosome *22* (CROCE *et al.* 1987; BUDARF, CANAANI and EMANUEL 1988; HEISTERKAMP and GROFFEN 1988). Thus, it was possible that the mouse 3′ cDNA probe detected a *Bcr*-related locus in the mouse rather than the structural gene. We mapped the mouse *Bcr* cDNA probe using multiple restriction enzymes (data not shown), but all polymorphisms segregated to the same locus on chromosome *10*. Probes derived from exon 1 of the human *BCR* structural gene exhibit no homology with the three *BCR*-related loci (HEISTERKAMP, KNOPPEL and GROFFEN 1988). Thus, we mapped a human exon 1 probe (HEISTERKAMP, KNOPPEL and GROFFEN 1988) and observed no crossovers with the mouse *Bcr* cDNA probe. A mouse genomic probe homologous to the human exon 1 probe was cloned and mapped in the IB, as well. Again, the mouse genomic probe exhibited no crossovers with the first two probes. Since the exon 1 probes detect single copy sequences and do not cross-hybridize with the *BCR*-related loci in humans, we conclude that we have mapped the mouse homolog of the *Bcr* structural gene to chromosome *10*.

Several probes listed in Table 1 detected additional polymorphisms that did not segregate to mouse chromosome *10*. First, the probe for the *Braf* locus detected a 4.8-kb fragment that segregated independently of a polymorphic 8.2-kb fragment. The 4.8-kb fragment mapped to mouse chromosome *10* as indicated (Table 1, Figure 2). The 8.2-kb polymorphism was mapped to mouse chromosome *6* in 40 N_2 animals analyzed, and was designated *Braf-2*. The *Cos* anonymous mouse probe, p2351, detected polymorphic fragments of 4.2 kb and 3.0 kb. The 4.2-kb fragment mapped to mouse chromosome *10* and was designated *Cos-1*. The 3.0-kb fragment mapped to mouse chromosome *19* and was designated *Cos-x*. The *Cdc-2* probe detected 7.2-kb and 5.2-kb polymorphic fragments that segregated independently of a 5.0-kb pol-

TABLE 1

Loci mapped in interspecific backcross mice

Locus	Gene name	Probe	Enzyme	Restriction fragment sizes in kb	
				C57BL/6J	*Mus spretus*
Act-2	*Actin-related gene-2*	β2000	*Hin*dIII	32, 17.5, 14.0, 12.0, 9.5, 8.9, 8.1, 6.8, 6.4, 5.5, 3.9, 3.6, 3.3, 3.0, 2.3, 2.0, 1.9, 1.7	28,[a] 17.5, 16.5, 13.0,[b] 11.0,[c] 9.5, 7.7, 7.6, 6.8, 5.0,[d] 4.7, 4.6, 3.9, 3.6, 3.3, 3.0, 2.7, 2.4,[c] 2.3, 2.0, 1.9, 1.4[a]
Ahi-1	*Abelson helper virus integration site-1*	p2-1	*Taq*I	7.1	5.8
Bcr	*Breakpoint cluster region gene*	Mouse cDNA	*Taq*I	3.0, 2.3, 1.8, 0.3	3.6, 2.6, 1.4, 0.8
		Mouse genomic	*Sph*I	8.8	4.8
		Human exon 1	*Taq*I	2.1	1.1
Braf	*Braf transforming gene*	pEX	*Bam*HI	16.5, 13.0, 11.0, 6.9, 6.2	16.5, 11.0, 8.2,[f] 4.8
Cdc-2a	*Cell division cycle control protein* homolog	C1-BS	*Eco*RI	23.0, 4.2, 2.2	7.2, 5.5, 5.0,[g] 2.2
pg^{rha}	Transgenic integration at the *pygmy* locus		*Pvu*II	4.2	2.2
Col6a-1	*α1(VI) collagen*	p18	*Pvu*II	7.9, 2.2, 1.4	4.2, 2.2, 1.4
Col6a-2	*α2(VI) collagen*	p1	*Pvu*II	9.2	5.7, 3.8
Cos-1	Anonymous mouse probe	p2351	*Pst*I	3.7, 0.5	4.2, 3.0,[h] 0.5
Esr	*Estrogen receptor*	pOR3	*Taq*I	5.6, 3.8, 3.2, 2.5, 2.3	5.6, 3.8, 3.2, 2.5, 2.3, 1.3
Fyn	*Fyn proto-oncogene*	Human fyn	*Bgl*I	6.9, 4.0, 3.3	6.9, 5.5, 3.3
Gli	*Glioblastoma oncogene*	pMGLI-RS	*Pst*I	4.2	3.6
Ifg	*Interferon-γ*	MγIFN	*Pvu*II	1.4, 0.5	4.2, 0.5
Igf-1	*Insulin-like growth factor-1*	pmigf1-2	*Taq*I	5.9, 1.8	3.1, 2.7, 1.9
Myb	*Myb proto-oncogene*	Mouse myb	*Bam*HI	10.1	21.0
Pah	*Phenylalanine hydroxylase*		*Bgl*I	8.6, 7.9, 6.7, 3.0, 2.8, 1.5	8.6, 7.9, 6.7, 2.8, 1.7
Ros-1	*Ros-1 proto-oncogene*	pSc3.2/23	*Pvu*II	8.2, 6.1, 5.3, 4.3, 3.6	9.6, 4.3, 3.6
S100b	*S100 protein, β subunit*	pHS100/2.2	*Pst*I	5.4	3.4

The 18 loci mapped in the 1B are shown. The RFLPs used for determining segregation in the backcross progeny are underlined.
[a] These two RFLPs mapped to two distinct loci on chromosome 6.
[b] This RFLP mapped to chromosome *5*.
[c] This RFLP mapped to the *X* chromosome.
[d] This RFLP mapped to chromosome *17*.
[e] This RFLP mapped to chromosome *8* (Ceci *et al.* 1990).
[f] This RFLP mapped to chromosome *6*.
[g] This RFLP mapped to chromosome *17*.
[h] This RFLP mapped to chromosome *19*.
[a–d,f–h] M. J. Justice, L. D. Siracusa, L. F. Lock, N. G. Copeland and N. A. Jenkins, unpublished results.

ymorphic fragment. The 7.2-kb and 5.2-kb fragments did not recombine and mapped to chromosome *10*, defining the locus designated *Cdc-2a* (Table 1, Figure 2). The 5.0-kb fragment mapped to chromosome *17*, defining a locus we designated *Cdc-2b*. The *Braf-2* and *Cos-x* RFLPs could be distinguished from the *Braf* and *Cos-1* RFLPs, respectively, by fainter hybridization intensities as well as by washing the filters at a higher stringency (0.1 × SSCP, 0.1% SDS for 1 hr at 65° for *Cos*; 0.3 × SSCP, 0.1% SDS for 1 hr at 65° for *Braf*). Under these conditions, the probes were selectively removed from the *Braf-2* and *Cos-x* fragments, but remained bound to the *Braf* and *Cos-1* fragments. The *Braf-2* locus is distinct from the *c-raf* locus on chromosome *6* and may represent a *raf*-related gene or pseudogene. Likewise, the *Cos-x* locus on chromosome *19* may be a *Cos-1*-related gene or pseudogene. The mouse genome may contain multiple *Cdc-2* loci; thus, the *Cdc-2a* and *Cdc-2b* loci may each represent an

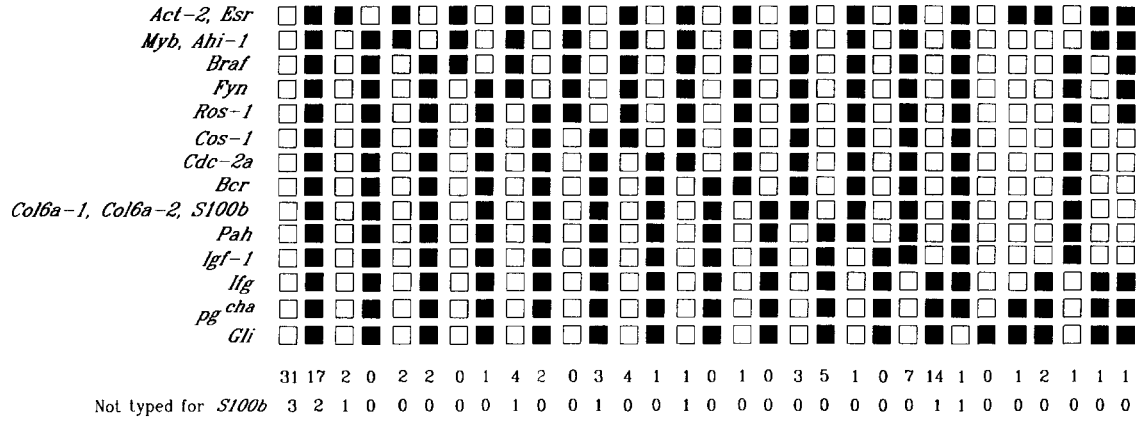

FIGURE 1.—Segregation of alleles in the (C57BL/6J × *M. spretus*)F_1 × C57BL/6J IB progeny. Genes mapped in the analysis are shown on the left. Each column represents the chromosome identified in the N_2 progeny that was inherited from the (C57BL/6J × *M. spretus*)F_1 female parent. The black boxes represent the presence of a C57BL/6J allele, and the open boxes represent the presence of a *M. spretus* allele. The total number of offspring inheriting each type of chromosome is shown at the bottom.

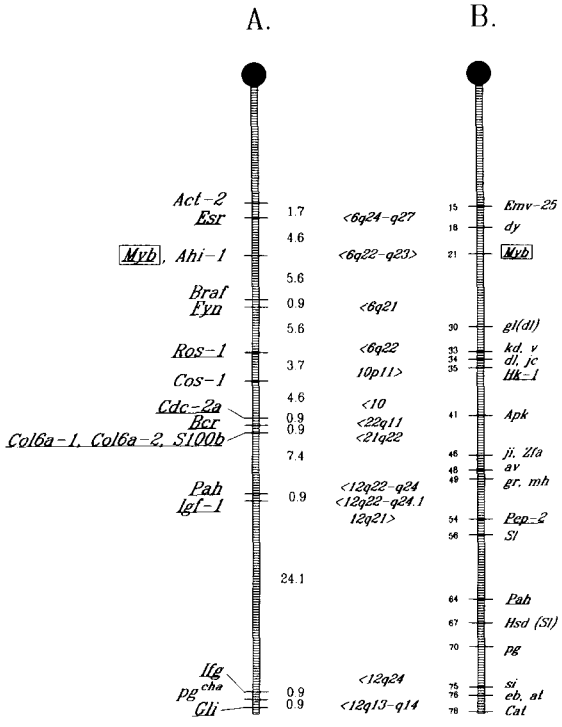

FIGURE 2.—Linkage maps of mouse chromosome *10*. The chromosome in A shows the loci mapped in the current study, with distances between loci given in cM. The chromosome in B shows the August 1989 version of the chromosome *10* linkage map compiled by M. T. DAVISSON, T. H. RODERICK, A. L. HILLYARD and D. P. DOOLITTLE as provided from GBASE, a computerized database maintained at The Jackson Laboratory, Bar Harbor, Maine (personal communication). This map is based on a compilation of data from genetic crosses among laboratory mouse strains, recombinant inbred strains, and IBs. The two linkage maps were aligned at the *Myb* locus, highlighted by a box on each map. Mouse genes that have been mapped in humans are underlined. Locations of these genes on human chromosomes are shown in the middle; arrowheads point to the locus that has been mapped in humans.

independent *Cdc-2* homolog (J. CORDEN, unpublished results).

The mouse genome contains >20 *actin*-related loci (MINTY *et al.* 1983). The chicken *β-actin* probe identified numerous RFLPs in *Hin*dIII digests that segregated independently (Table 1). The probe is a full-length cDNA containing conserved sequences that are expected to cross-react with many different actin genes (CLEVELAND *et al.* 1980). This probe is also expected to detect the *β-actin* structural locus, which maps to mouse chromosome *5* (CZOSNEK *et al.* 1983). Seven of the *M. spretus*-specific RFLPs corresponding to *actin*-related loci segregated to six chromosomes; two mapped to distinct locations on mouse chromosome *6*, and one mapped to each of mouse chromosomes *5*, *8*, *10*, *17* and *X* (CECI *et al.* 1990; this manuscript). We have designated the *actin*-related locus on mouse chromosome *10 Act-2*. No *actin* genes, *actin*-related structural genes, or *actin* pseudogenes have previously been mapped to mouse chromosome *10*.

The segregation of many alleles on chromosome *10* from the (C57BL/6J × *M. spretus*)F_1 female parent differed significantly from the 1:1 ratio expected if each allele was transmitted in a normal Mendelian fashion. Using a G test on partitioned samples to test statistical significance (SOKAL and ROHLF 1981), the transmission ratios were significantly different at a 90% confidence level from a 1:1 ratio for all loci except *Act-2*, *Esr*, *Ifg*, pg^{cha} and *Gli* (Table 2).

DISCUSSION

The molecular genetic linkage map establishes the orientation of 18 loci on mouse chromosome *10* using a single IB. The *Act-2*, *Bcr*, *Braf*, *Cdc-2a*, *Esr*, *Fyn*, *Gli*, *Igf-1* and *Ros-1* loci were mapped to mouse chromosome *10* for the first time. The *Ahi-1*, *Col6a-1*, *Col6a-2*, *Cos-1*, *Ifg*, *Pah* and *S100b* loci were regionally localized. The molecular markers mapped in this study span 63 cM, and thus extend along much of the predicted 78 cM of chromosome *10* (GREEN *et al.*

TABLE 2

A G test for allelic segregation in the interspecific backcross

Locus	No. homozygous C57BL/6J	No. heterozygous C57BL/6J /*M. spretus*	G_p value	*P* value
Act-2, Esr	48	60	1.34	<0.250
Myb, Ahi-1	43	65	4.51	<0.050
Braf	43	65	4.51	<0.050
Fyn	44	64	3.73	<0.100
Ros-1	42	66	5.38	<0.025
Cos-1	44	64	3.73	<0.100
Cdc-2a	41	67	6.32	<0.010
Bcr	40	68	7.34	<0.010
Col6a-1, Col6a-2	39	69	8.44	<0.005
Pah	41	67	6.32	<0.025
Igf-1	40	68	7.34	<0.010
Ifg	50	58	0.59	<0.500
pg^{cha}	51	57	0.33	<0.750
Gli	50	58	0.59	<0.500

The G_p values shown represent a G test carried out on partitioned samples at each locus on chromosome *10*. A G test for homogeneity of samples revealed that the samples were homogeneous across loci (SOKAL and ROHLF 1981).

1972; RODERICK and DAVISSON 1981), allowing molecular access to many regions of chromosome *10*. The map provides a framework for (1) mapping additional markers on mouse chromosome *10*, (2) revealing linkage relationships between mouse mutations and molecular probes, and (3) extending and refining homologies with human chromosomes.

Comparison with previous mapping results: It is possible to compare our molecular genetic linkage map with the composite genetic linkage map of T. H. RODERICK, M. T. DAVISSON, A. L. HILLYARD and D. P. DOOLITTLE (August 1989, personal communication). Previously, *Myb*, *Pah* and *pg* had been oriented on chromosome *10*. *Myb* was mapped 35.1 ± 5.6 cM proximal to *Steel* (*Sl*) in a mouse intraspecific linkage testing stock (TAYLOR and ROWE 1989). *Pah* mapped 32.0 ± 6.2 cM from *Myb* using IBs, although proximal-distal orientation was not determined (BODE *et al.* 1988). In addition, *Pah* had been localized by *in situ* hybridization analysis to chromosome *10*, band C2-D1 (LEDLEY *et al.* 1988). A translocation breakpoint involving *Steel* (*Sl*) had been mapped by *in situ* hybridization analysis to chromosome *10*, band D1-D2 (CACHEIRO and RUSSELL 1975). This suggests that *Sl* is distal of *Pah*; however, a different order is given on the composite linkage map (Figure 2B). The order shown on the composite linkage map (Figure 2B) is based on recombination frequencies between *Myb*, *Zfa* and *Pah* in an IB (MITCHELL *et al.* 1989). At this time, *Sl* and *Pah* have not been mapped relative to each other in a multilocus cross; such analysis would resolve this discrepancy. The *pg* locus was mapped 14.2 ± 4.0 cM from *Sl*, linked to *silver* (*si*), in intraspecific crosses (FALCONER and ISAACSON 1965). The distal location of pg^{cha} on the IB map is in agreement with the distal location of *pg* on the composite genetic linkage map.

Transmission ratio distortion: Analysis of the transmission of alleles from the (C57BL/6J × *M. spretus*)F_1 parent in the IB revealed a statistically significant deviation from the expected 1:1 Mendelian transmission of alleles at many loci on chromosome *10* (Table 2). This phenomenon is not restricted to our IB since transmission ratio distortions have been previously observed in IBs that involve *M. spretus* mice (BIDDLE 1987; SELDIN, HOWARD and D'EUSTACHIO 1989; J.-L. GUENET, personal communication), and for regions of chromosome *2* (SIRACUSA *et al.* 1989) and chromosome *4* (CECI *et al.* 1990) in our [(C57BL/6J × *M. spretus*)F_1 × C57BL/6J] IB. In our cross, transmission ratio distortion was not significant for the most proximal and distal loci on chromosome *10*. Differential survival of neonates can be ruled out as a cause of transmission ratio distortion in this IB since the mortality rate between birth and sacrifice was very low (6%). Thus, the transmission ratio distortion (TRD) on chromosome *10* must be due to effects occurring between meiosis in the heterozygous F_1 female parents and birth. TRD may be due to: (1) differential production or survival of oocytes, (2) differential fertilization efficiencies or (3) differential survival of embryos. The simplest explanation for the transmission ratio distortion on chromosome *10* is differential survival of embryos. It is likely that certain allelic combinations at a locus or at several loci in the central region of the chromosome have an adverse effect on survival of the C57BL/6J homozygotes or that heterozygotes have a selective survival advantage.

Homologies with human chromosomes: Mouse chromosome *10* exhibits four regions of synteny with human chromosomes. First, a 16.7-cM region of mouse chromosome *10* is syntenic with human chromosome *6q* (Figure 2). This syntenic group includes *ESR*, *MYB*, FYN and *ROS1*, which map to human chromosome *6q24-q27*, *6q22-q23*, *6q21* and *6q22*, respectively (GOSDEN, MIDDLETON and ROUT 1986; JANSSEN *et al.* 1986; NAGARAJAN *et al.* 1986; POPESCU *et al.* 1987; RABIN *et al.* 1987). Second, the localization of *Cdc-2a* near *hexokinase-1* (*Hk-1*) defines a small region of synteny with human chromosome *10* (SPURR *et al.* 1988; SCHWARTZ *et al.* 1984). Third, the *Col6a-1*, *Col6a-2* and *S100b* loci define a small region in the central part of the chromosome that is conserved on human chromosome *21*. Each of these loci has been mapped to human chromosome *21q22* (WEIL *et al.* 1988; ALLORE *et al.* 1988; MACDONALD *et al.* 1988). Finally, *PAH*, *IGF1*, *IFG*, *GLI*, and *peptidase B* (*PEPB*; *Pep-2* in mice) are conserved in a syntenic group on human chromosome *12q*. In humans, *PAH* maps to *12q22-q24*, *IGF1* maps to *12q22-q24.1*, *IFG* maps to *12q24*, *GLI* maps to *12q13-q14*, and *PEPB* maps to *12q21* (JONGSMA, HAGEMEIJER and MEERA KAHN

1975; TRENT, OLSON and LAWN 1982; NAYLOR *et al.* 1983; LIDSKY *et al.* 1985; MORTON *et al.* 1986; ARHEDEN *et al.* 1989). It is interesting to note that the regions of synteny with human chromosomes delimited by the loci on our molecular genetic linkage map (Figure 2A) combined with loci on the composite genetic linkage map that have been mapped in humans (Figure 2B) minimize interruptions of syntenic groups between mice and humans.

The localization of the mouse homolog of *Bcr* to chromosome *10* identifies the first homology segment with human chromosome *22q* on mouse chromosome *10*. Genes that map to human chromosome *22q* are widely dispersed in the mouse. For example, the *immunoglobulin lambda light chain* (*IGL*; *Igl-1* in mice), the *PDGFB/SIS proto-oncogene*, and *BCR* all map to bands *q11-q13* of human chromosome *22* (KAPLAN and CARRITT 1987). However, *Igl-1* maps to mouse chromosome *16* (EPSTEIN *et al.* 1986), *Sis* maps to mouse chromosome *15* (HUPPI, DUNCAN and POTTER 1988), and *Bcr* maps to mouse chromosome *10*.

Loci affecting tumor incidence: *Ahi-1* is a common site of helper virus integration in Abelson murine leukemia virus-induced pre-B-cell lymphomas, and has been proposed by POIRIER, KOZAK and JOLICOUER (1988) to represent a novel locus causally associated with pre-B-cell lymphomas. POIRIER, KOZAK and JOLICOUER (1988) mapped *Ahi-1* to chromosome *10* using somatic cell hybrids, and compared *Ahi-1* to *Myb*, a proto-oncogene associated with B-cell lymphomas in chickens (KANTER, SMITH and HAYWARD 1988), and with hematopoietic tumors in mice and humans (SHEN-ONG *et al.* 1984; OHYASHIKI *et al.* 1988); however, no relationships between *Ahi-1* and *Myb* were established. It is possible that a relationship between the two probes was not detected, since the entire *Myb* coding region was not used as a probe in these studies (POIRIER, KOZAK and JOLICOUER 1988). We have observed no crossovers in 169 animals between *Ahi-1* and *Myb*, giving an upper 95% confidence limit of 1.7 cM between the two loci. Therefore, *Ahi-1* may represent a region within or near the *Myb* locus, and viral integration in *Ahi-1* may alter *Myb* expression leading to neoplastic disease. Alternatively, *Ahi-1* may be closely linked to *Myb*, but represent a novel proto-oncogene associated with pre-B-cell lymphomas. The close linkage of *Ahi-1* and *Myb* suggests that further studies are necessary to determine whether *Ahi-1* is a novel proto-oncogene or whether viral integrations at *Ahi-1* affect *Myb* expression.

The *ESR*, *MYB*, *FYN* and *ROS1* loci all map to human chromosome *6q*, a region that is commonly associated with tumor-specific chromosome rearrangements (MITELMAN 1983; BERGER, BLOOMFIELD and SUTHERLAND 1985). *Esr* has been implicated in the progression of many breast neoplasias (YOUNG, EHRLICH and EINHORN 1980). *Myb* is the cellular homolog of the transforming sequence of avian myeloblastosis virus (FRANCHINI *et al.* 1983; LEPRINCE *et al.* 1983). *Fyn* (also called *Syn*, *Slk* and *Syr*) was identified as a human *src*-related gene with transforming properties (SEMBA *et al.* 1986; KAWAKAMI, PENNINGTON and ROBBINS 1986; YOSHIDA *et al.* 1986). *Ros-1* is the mouse cellular homolog of the transforming gene of the avian sarcoma virus, UR2 (BIRCHMEIER *et al.* 1986). It is likely that *Braf*, a transforming gene with homologies to c-*raf* and A-*raf* (IKAWA *et al.* 1988), will also map to human chromosome *6q*, based on its linkage with *Fyn* and *Ros-1* in mice.

Translocations and deletions associated with human chromosome *6q* are associated with numerous malignancies, including teratocarcinomas (OOSTERHUIS *et al.* 1985), hematologic neoplasias (MITELMAN 1983; BERGER, BLOOMFIELD and SUTHERLAND 1985), malignant melanomas (BECHER, GIBAS and SANDBERG 1983; PATHAK, DRWINGA and HSU 1983; TRENT, ROSENFELD and MEYSKENS 1983), and ovarian carcinomas (WAKE *et al.* 1980). Human chromosome *6q21* contains a fragile site that may account for some of these chromosomal abnormalities in human neoplasias (YUNIS and SORENG 1984; HEIM and MITELMAN 1989; POPESCU *et al.* 1987). At this time, only the *Myb* proto-oncogene has been causally associated with neoplasia in mice (SHEN-ONG *et al.* 1984). Further studies may reveal the role of genes localized to this region in mouse neoplastic disease.

The *breakpoint cluster region* gene (*BCR*) on human chromosome *22* is linked to the *ABL* oncogene from chromosome *9* in the *t(9;22)(q34;q11)* translocation that identifies the Philadelphia (Ph) chromosome (NOWELL and HUNGERFORD 1960). The Ph chromosome is the cytogenetic hallmark of chronic myelogenous leukemia, and is also found in acute lymphoblastic leukemias (NOWELL and HUNGERFORD 1960; SANDBERG *et al.* 1980; PRIEST *et al.* 1980; HERMANS *et al.* 1987). The translocation results in a BCR-ABL fusion protein that is causally associated with human neoplastic disease. To date, the region of mouse chromosome *10* containing *Bcr* has not been causally implicated in murine neoplastic disease.

Molecular markers that map near mouse mutations: The map locations of several genes suggest that they may be candidates for existing mouse mutations. For example, the *S100b* locus maps in a region that contains the *jittery* (*ji*) mutation. S100 is a calcium-binding protein that is structurally similar in the calcium-binding domains to calmodulin (MOORE 1965; MARSHAK, WATTERSON and VAN ELDIK 1981; PATEL and MARANGOS 1982; DONATO 1985; ZIMMER and VAN ELDIK 1986). It is widely distributed in the nervous system of vertebrates (MOORE 1965; KESSLER,

LEVINE and FASMAN 1968; CALISSANO, MOORE and FRIESEN 1969) and accumulates during the maturation of the mammalian brain (ZUCKERMAN, HERSCHMAN and LEVINE 1970; CICERO *et al.* 1972). Homozygous *ji/ji* mice exhibit a rapidly progressive neuromuscular incoordination at 10–16 days of age manifested by seizures and tetany, followed by death by 4 weeks of age (DEOME 1945; summarized by GREEN 1989). The basis for the neuromuscular abnormality in *ji/ji* mice has not been determined. The seizures and tetany exhibited by *ji/ji* mice are consistent with abnormalities in a calcium-binding neuronal protein. Humans affected by trisomy 21 (Down syndrome) exhibit neuropathological changes associated with the aging brain consisting of neurofibrillary tangles, senile plaques, and neuronal loss. Several genes that may play a role in the neurologic abnormalities characterizing Down syndrome have been assigned to human chromosome *21*, including *S100b* (TANZI *et al.* 1987; ST. GEORGE-HYSLOP *et al.* 1987; ALLORE *et al.* 1988). If *ji* is homologous to *S100b*, the *ji* mutation may be useful for understanding the neuropathological changes of Down syndrome. Note that the region of human chromosome *21* that is trisomic in Down syndrome is dispersed in the mouse. Markers on human chromosome *21* that are trisomic in Down syndrome map to mouse chromosomes *16*, *17* and *10* (summarized by NADEAU 1989). If *S100b* does not represent the homolog of *ji*, it may be useful for gaining molecular access to the *ji* mutation.

The *Fyn* or *Ros-1* proto-oncogenes may be candidates for the *grey-lethal* (*gl*) mutation on chromosome *10*. The *Fyn* and *Ros-1* genes are members of the *src*-related family of cellular oncogenes (reviewed by J. M. BISHOP 1985), many of which are involved in the control of cell proliferation and differentiation (DOWNWARD *et al.* 1984; SHERR *et al.* 1985; NAGARAJAN *et al.* 1986). *Ros-1* is expressed in numerous human hematopoietic tumor cell lines (DE BOTH *et al.* 1989) and likely encodes a growth factor receptor (RABIN *et al.* 1987). *Fyn*-encoded proteins have been found in normal human hematopoietic cells (KAWAKAMI, FURUE and KAWAKAMI 1989). Mice homozygous for the *gl* mutation are osteopetrotic because they lack the ability for secondary bone resorption and have an increased rate of bone deposition (GRUNEBERG 1936; BATEMAN 1954; MARKS and WALKER 1969; summarized by GREEN 1989). The basic defect caused by *gl* is likely to be in cells derived from bone marrow or spleen that control the activity of osteoclasts (WALKER 1975a,b). *Fyn* and *Ros-1* are potential candidate genes for the *gl* mutation, based on their expression in hematopoietic cells and their probable role in controlling cell growth and/or differentiation. If neither *Fyn* nor *Ros-1* represents the homolog of *gl*, they may be useful for gaining molecular access to the *gl* mutation.

Mouse models of human syndromes: By comparing the mouse and human linkage maps, we can predict the locations of certain loci or syndromes in the human genome. The mouse mutation *kidney disease* (*kd*) has been proposed to be a model of the human kidney disease nephronophthisis (LYON and HULSE 1971). Both the human and mouse diseases exhibit a degenerative destruction of the kidneys involving tubules and glomeruli (LYON and HULSE 1971; FANCONI *et al.* 1951; GISELSON *et al.* 1970). Nephronophthisis is an autosomal recessive disorder in humans, but has not been mapped to a human chromosome. If nephronophthisis is the human homolog of *kd*, it should map to either human chromosome *6* or human chromosome *10*, based on the location of *kd* in the mouse. Thus, the *Myb*, *Ros-1*, *Fyn*, *Hk-1* (Figure 2B), *Cos-1* and *Cdc-2a* molecular markers may be useful probes to use in linkage studies in families affected by nephronophthisis. Pedigrees of families affected by nephronopthisis can be followed by RFLP analysis using these molecular markers. Identification of close linkage between nephronophthisis and one of the molecular markers may be useful in preliminary diagnosis of this disease in humans.

The mouse *pygmy* (*pg*) mutation is a useful model for the human non-growth hormone-deficient syndromes (SINHA *et al.* 1979; XIANG, BENSON and CHADA 1990), and has been hypothesized to be a model to investigate the biochemical defect of the human African pygmy (RIMOIN and RICHMOND 1972). Mice homozygous for a transgenic integration at pg^{cha} are smaller than normal littermates. After mapping a probe flanking the pg^{cha} transgenic integration in the IB to the distal region of chromosome *10*, which contains the *pg* mutation, subsequent studies revealed that the pg^{cha} mutation was an allele of *pg* (XIANG, BENSON and CHADA 1990). Human African pygmies and homozygous *pg/pg* mice fail to respond to exogenous growth hormone (RIMOIN *et al.* 1969; RIMOIN and RICHMOND 1972; SINHA *et al.* 1979). In isolated cases, an absence of *IGF1* has been associated with the human African pygmy, leading to the proposal that *IGF1* may be the principal growth factor lacking in African pygmies (MERIMEE, ZAPF and FROESCH 1981; MERIMEE *et al.* 1987). However, this proposal has been criticized on the basis of possible nutritional effects on *IGF1* in human pygmies (UNDERWOOD *et al.* 1982). *Igf-1* is unlikely to be directly involved in the mouse pygmy syndrome, since pg^{cha} represents an allele of *pg*, and *Igf-1* and pg^{cha} are separated by 25.0 cM in the mouse. The chromosomal location of pg^{cha} within a large region of synteny conserved on human chromosome *12q* suggests that the human African pygmy syndrome will map to human chromosome *12q*. Fur-

ther studies of the mouse model may aid in understanding the biochemical basis of the human African pygmy.

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