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, Ber, Braf, Cdc-2a, Cal6a-1, Cal6a-2, Cad-1, Est, Fyn, Gli, Igf-1, Myb, Pah, pgiso, 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 Houssman 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 (Brutton et al. 1988; Winter 1988; Ryder-Cook et al. 1988; Glaser and Houssman 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 F1 females and sterile F1 males (Bonhomme et al. 1984). The F1 females can then be backcrossed to generate the N2 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 JOLICOUR; 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/6) × M. spre tus F1, C57BL/6 JIB, an actin-related locus (Act-2), the breakpoint cluster region gene (Bcr), the Braf transforming gene (Braf), a cell division cycle control protein gene (Cdc2a), 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^-), 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/6) × M. spre tus] F1 × C57BL/6 J] 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 PstI-HindIII genomic fragment cloned in pUC18 (p2-1; POIRIER, KOZAK and JOLICOUR 1988) that was a gift from P. JOLICOUR [Clinical Research Institute of Montreal (Montreal, Quebec, Canada)].

The probe for the actin-related locus (Act-2) was a chicken full-length cDNA cloned in pBR322 (B2000; 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 EcoRI 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) EcoRI/HindIII 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 Xbal/BglII fragment from exon 1 of the BCR gene (probe 1; HEISTERKAMP, KNOPEL and GROFFEN 1988).

The probe for the Braf transforming gene (Braf) was a human cDNA EcoRI-Xhol 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 (Cdc2a) was a mouse cDNA EcoRI 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. 1982) and collagen α2(VI) (Col6a-2) (p1; CHU et al. 1987) were human cDNA EcoRI 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 EcoRI fragment (p235; 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 EcoRI 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 NcoI 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 EcoRI/HindIII 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 BamHI 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 EcoRI 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 Xbal 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 (SAIL 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^-) 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 Sall fragment cloned in pAT (pS3.2/23; 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 EcoRI-HindIII 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
Act-2 loci; 3 crossovers were detected in a total of 179 recombinant chromosomes to the total number of N2 progeny were also analyzed for the Esr and pairwise combination for the Ahi-1 and Myb loci; no Actin, a nick translation kit (Amersham) for whole plasmids or a analysis. Each backcross animal appeared to be either progeny shown in Figure 1 spretus)F1 of DNAs from NZ progeny of a [(C57BL/6J X spretus)X 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 N2 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, Ber, (Col6a-1, Col6a-2, S100b), Pah, Igf-1, Igf, pg<sup>ha</sup> and Gli] was determined by the analysis of 108 N2 progeny (Figure 1). Note that the S100b locus was typed for a subset of the NZ progeny shown in Figure 1; no crossovers were observed between the S100b and Col6a-1/Col6a-2 loci in 97 N2 progeny, giving an upper 95% confidence limit of 3.0 centiMorgans (cM) between S100b and Col6a-1/Col6a-2. Additional N2 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 N2 progeny, giving an upper 95% confidence limit of 1.7 cM between Ahi-1 and Myb. Additional N2 progeny were also analyzed for the Esr and Act-2 loci; 3 crossovers were detected in a total of 179 N2 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–Ber–1/108–(Col6a-1–0/108–Col6a-2–0/97–S100b)–8/108–Pah–1/108–Igf-1–26/108–Igf-1–1/108–pg<sup>ha</sup>–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–Ber–0.9 ± 0.9–(Col6a-1, Col6a-2, (S100b))–7.4 ± 2.5–Pah–0.9 ± 0.9–Igf-1–24.1 ± 4.1–Igf–0.9 ± 0.9–pg<sup>ha</sup>–0.9 ± 0.9–Gli.

The Ber 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 Ber cDNA probe. A mouse genomic probe homologous to the human exon 1 probe was cloned and mapped in the 1B, 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 N2 animals analyzed, and was designated Braf-2. The Cos anonymous mouse 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-
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The 18 loci mapped in the IB are shown. The RFLPs used for determining segregation in the backcross progeny are underlined.

* These two RFLPs mapped to two distinct loci on chromosome 6.
* This RFLP mapped to chromosome 5.
* This RFLP mapped to the X chromosome.
* This RFLP mapped to chromosome 17.
* This RFLP mapped to chromosome 8 (Ceci et al. 1990).
* This RFLP mapped to chromosome 8.
* This RFLP mapped to chromosome 6.
* This RFLP mapped to chromosome 17.
* This RFLP mapped to chromosome 19.

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-9 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 X SSCP, 0.1% SDS for 1 hr at 65° for Cos; 0.3 X 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-1 fragments, but remained bound to the Braf and Cos-1 fragments. The Braf-2 locus is distinct from the craf locus on chromosome 6 and may represent a raf-related gene or pseudogene. Likewise, the Cos-1 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)F1 × C57BL/6J IB progeny. Genes mapped in the analysis are shown on the left. Each column represents the chromosome identified in the N2 progeny that was inherited from the (C57BL/6J × M. spretus)F1 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. Hilliard 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 HindIII 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)F1 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 Rohlff 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, Pgpha 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, Ifg-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.
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. DOOLTITTE (August 1989, personal communication). Previously, Myb, Pah and pg had been oriented on chromosome 10. Myb was mapped 55.1 ± 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 on the composite genetic linkage map.

Transmission ratio distortion: Analysis of the transmission of alleles from the (C57BL/6J × M. spretus)F1 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)F1 × 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 F1 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; JANSSSEN 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 Colba-1, Colba-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 12q22 (WEL et al. 1988; ALLORE et al. 1988; MACDONALD et al. 1988). Finally, PAH, IGF1, IGF, 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 12q22-2q24, IGF maps to 12q24, GLI maps to 12q14-q14, and PEPB maps to 12q21 (JONSM, HAGEMEIJER and MEERA KAHN

### Table 2

A G test for allelic segregation in the interspecific backcross

<table>
<thead>
<tr>
<th>Locus</th>
<th>No. homozygous C57BL/6J</th>
<th>No. heterozygous C57BL/6J × M. spretus</th>
<th>Gy value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Act-2, Eyr</td>
<td>48</td>
<td>60</td>
<td>1.34</td>
<td>&lt;0.250</td>
</tr>
<tr>
<td>Myb, Ahi-1</td>
<td>43</td>
<td>65</td>
<td>4.51</td>
<td>&lt;0.050</td>
</tr>
<tr>
<td>Braf</td>
<td>43</td>
<td>65</td>
<td>4.51</td>
<td>&lt;0.050</td>
</tr>
<tr>
<td>Fyn</td>
<td>44</td>
<td>64</td>
<td>3.73</td>
<td>&lt;0.100</td>
</tr>
<tr>
<td>Ros1-1</td>
<td>42</td>
<td>66</td>
<td>5.38</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Cos-1</td>
<td>44</td>
<td>64</td>
<td>5.73</td>
<td>&lt;0.100</td>
</tr>
<tr>
<td>Gdc-2a</td>
<td>41</td>
<td>67</td>
<td>6.32</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td>Bcr</td>
<td>40</td>
<td>68</td>
<td>7.34</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td>Col6a-1, Col6a-2</td>
<td>39</td>
<td>69</td>
<td>8.44</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Pah</td>
<td>41</td>
<td>67</td>
<td>6.32</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Igf1</td>
<td>40</td>
<td>68</td>
<td>7.34</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td>Ifg</td>
<td>50</td>
<td>58</td>
<td>0.59</td>
<td>&lt;0.500</td>
</tr>
<tr>
<td>pg&lt;sup&gt;+&lt;/sup&gt;</td>
<td>51</td>
<td>57</td>
<td>0.33</td>
<td>&lt;0.750</td>
</tr>
<tr>
<td>GlI</td>
<td>50</td>
<td>58</td>
<td>0.59</td>
<td>&lt;0.500</td>
</tr>
</tbody>
</table>

The Gy 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).
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), Six 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). Est 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, Silk and Syr) was identified as a human src-related gene with transforming properties (SEMSA 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 1986), 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; SIMM and VAN ELDIK 1986). It is widely distributed in the nervous system of vertebrates (MOORE 1965; KESSLER.
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; FANCONE 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 *Mby, 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 nephronophthisis 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*<sup>ha</sup> are smaller than normal littersmates. After mapping a probe flanking the *pg*<sup>ha</sup> transgenic integration in the 1B to the distal region of chromosome 10, which contains the *pg* mutation, subsequent studies revealed that the *pg*<sup>ha</sup> 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 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*<sup>ha</sup> represents an allele of *pg*, and *Igf-1* and *pg*<sup>ha</sup> are separated by 25.0 cM in the mouse. The chromosomal location of *pg*<sup>ha</sup> 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 understand-

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