A Comprehensive Genetic Map of Murine Chromosome *11* Reveals Extensive Linkage Conservation Between Mouse and Human

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ABSTRACT

Interspecific backcross animals from a cross between C57BL/6J and *Mus spretus* mice were used to generate a comprehensive linkage map of mouse chromosome *11*. The relative map positions of genes previously assigned to mouse chromosome *11* by somatic cell hybrid or genetic backcross analysis were determined (*Erbb, Rel, Il-3, Csfgm, Trp53-1, Evi-2, Erba, Erbb-2, Csfg, Myhs, Cola-1, Myla, Hox-2* and *Pkca*). We also analyzed genes that we suspected would map to chromosome *11* by virtue of their location in human chromosomes and the known linkage homologies that exist between murine chromosome *11* and human chromosomes (*Mpo, Ngfr, Pdgfr* and *Fms*). Two of the latter genes, *Mpo* and *Ngfr*, mapped to mouse chromosome *11*. Both genes also mapped to human chromosome *17*, extending the degree of linkage conservation observed between human chromosome *17* and mouse chromosome *11*. *Pdgfr* and *Fms*, which are closely linked to *Il-3* and *Csfgm* in humans on chromosome *5*, mapped to mouse chromosome *18* rather than mouse chromosome *11*, thereby defining yet another conserved linkage group between human and mouse chromosomes. The mouse chromosome *11* linkage map generated in these studies substantially extends the framework for identifying homologous genes in the mouse that are involved in human disease, for elucidating the genes responsible for several mouse mutations, and for gaining insights into chromosome evolution and genome organization.

ESTABLISHMENT of comprehensive multilocus linkage maps for mouse chromosomes will provide important tools for studying genome organization and linkage conservation between species. Extensive linkage maps will also aid in the identification of animal models of genes important in human development and disease, as well as in the accurate placement of genes along the total length of a chromosome. A recent example of the identification of an animal model for human disease via chromosome mapping is the congenital goiter, *cog*, mutation in the mouse (TAYLOR and ROWE 1987). Hereditary hypothyroidism in humans has been associated with defects in the thyroglobulin, *TG*, locus (VAN HERLE, VASSART and DUMONT 1979). This knowledge enabled TAYLOR and ROWE (1987) to demonstrate that the *cog* mutation in mice is closely linked to the *Tg* locus and may be a mutation in the *Tg* structural locus. Another example of the value of cross-species mapping has been demonstrated for the mammalian *X* chromosome. This chromosome has been highly conserved throughout evolution (OHNO 1969); mapping comparisons have demonstrated that the human *X* chromosome can be made colinear with the murine *X* chromosome by a minimum of five inversion events (AVNER *et al.* 1988). Thus, identification and mapping of a mutation on the *X* chromosome of one mammalian species would enable the identification of homologous loci on the *X* chromosome of another mammalian species.

The ability to perform a multilocus linkage cross with the mouse has been hindered because most inbred mouse strains are closely related (FERRIS, SAGE and WILSON 1982). The relatedness between inbred strains makes identification of restriction fragment length polymorphisms (RFLPs) or protein polymorphisms for multiple loci difficult. However, a powerful genetic technique for establishing genetic linkage maps has been recently described (ROBERT *et al.* 1985; reviewed in AVNER *et al.* 1988). This technique, analysis of the segregation of polymorphic alleles in interspecific backcross progeny, enables the simultaneous mapping of numerous loci in a single cross. The strength of the technique resides in the evolutionary distance between the two parental species used in these crosses, *Mus domesticus* (represented by C57BL/6J in these studies) and *Mus spretus* (BRITTON and THALER 1978). This evolutionary distance, 3–5 million years (BONHOMME *et al.* 1984), has allowed for the accumulation of DNA sequence differences between the two species; these sequence differences are

revealed in the form of RFLPs. Numerous examples of linkage maps generated from interspecific mouse backcrosses have been reported (AMAR *et al.* 1985; AVNER *et al.* 1987; BUCAN *et al.* 1986; BUCHBERG *et al.* 1988; DAUTIGNY *et al.* 1986; ROBERT *et al.* 1985; SELDIN *et al.* 1987; WEYDERT *et al.* 1985). With the exception of the proximal region of chromosome *17* (M. HAMMER and L. M. SILVER, personal communication), no large chromosome alterations have been found to exist between *M. spretus* and *M. domesticus.* Thus, the maps generated by interspecific backcross analyses are colinear with linkage maps generated using standard laboratory mice (reviewed in AVNER *et al.* 1988).

We have been interested in developing an extensive linkage map of mouse chromosome *11* because of the large number of proto-oncogenes, growth factors, growth factor receptors and common viral integration sites that are known to map to mouse chromosome *11.* Our previously reported linkage analysis of mouse chromosome *11*, which included the genes *Erbb, Rel, Il-3, Csfgm, Trp53-1, Evi-2, Erba, Erbb-2* and *Csfg* (BUCHBERG *et al.* 1988), has now been extended by examining the linkage of these and several additional loci in 144 N2 interspecific backcross progeny. The additional loci examined include: 1) loci defined by the viral integration sites *Pad-1, Mov-9* and *Int-4* (A. SONNENBERG, personal communication; RIJSEWIJK *et al.* 1987; CHUMAKOV *et al.* 1982; H. ROELINK and R. NUSSE, personal communication; NUSSE 1988); 2) structural genes *Myhs, Cola-1, Mpo* and *Myla* (WEYDERT *et al.* 1983; HARBERS *et al.* 1984; MORISHITA *et al.* 1987; BARTON *et al.* 1988); 3) growth factor receptors and protein kinase genes *Ngfr, Pdgfr, Fms* and *Pkca* (JOHNSON *et al.* 1986; PARKER *et al.* 1986; YARDEN *et al.* 1986; GISSELBRECHT *et al.* 1987); and 4) a gene potentially important in development, *Hox-2* (HAUSER *et al.* 1985; JOYNER *et al.* 1985; HART *et al.* 1988). The results of the mapping analysis have revealed further extensive linkage homology between mouse chromosome *11* and human chromosome *17* as well as several other human chromosomes. These results also aid in identifying genes in the mouse that are homologous to genes involved in human disease.

MATERIALS AND METHODS

Mice: The C57BL/6J inbred strain is maintained at the NCI-Frederick Cancer Research Facility. The *Mus spretus* mice were at the F_7, F_9, F_{10} or F_{12} generation of inbreeding and were a gift from E. M. EICHER [The Jackson Laboratory (Bar Harbor, Maine)]. The interspecific backcross [(C57BL/6J × *Mus spretus*) × C57BL/6J] was performed at the NCI-Frederick Cancer Research Facility as described previously (BUCHBERG *et al.* 1988); a total of 144 N2 progeny were analyzed for this report.

DNA isolation and Southern blot analyses: High molecular weight genomic DNAs were prepared from frozen mouse tissues (JENKINS *et al.* 1982). Restriction endonuclease digestion, agarose gel electrophoresis, Southern blot transfer, hybridization and washes were performed as described (JENKINS *et al.* 1982; BUCHBERG *et al.* 1988).

Probes: The probes used and their corresponding loci are listed in Tables 1 and 2.

Statistical analysis: Statistical analysis of the recombination frequencies from the results of interspecific backcrosses was performed by calculating the maximum likelihood estimates of linkage parameters as described by GREEN (1981), using the computer program "SPRETUS MADNESS" (developed by D. DAVE [Data Management Services, Inc., Frederick, Maryland] and A. M. BUCHBERG). Gene order was confirmed by the maximum likelihood analysis (BISHOP 1985). Statistical analysis of the number of double recombinants was performed by W. G. ALVORD (Data Management Services, Inc., Frederick, Maryland); the statistic test used was a large sample normal approximation to the binomial distribution.

RESULTS

Identification of RFLPs and mapping of loci on chromosome *11*: Genomic DNA from C57BL/6J and *M. spretus* animals was digested with several restriction endonucleases and analyzed by Southern blot hybridization using probes for the loci listed in Table 1 to identify RFLPs useful for gene mapping. The strength of interspecific backcross analysis was realized in these studies in that at least one informative RFLP was identified for each probe (Table 1).

The segregation of *M. spretus* alleles in 144 [(C57BL/6J × *M. spretus*) × C57BL/6J] backcross progeny was then followed by Southern blot analysis using each of the probes listed in Table 1. The results of the segregation analysis are summarized in Figure 1. Mice were either heterozygous for the C57BL/6J and *M. spretus* alleles or homozygous for the C57BL/6J allele at each locus. No novel genotypes were observed. The frequency of C57BL/6J and *M. spretus* alleles for all of the loci examined in the N2 progeny did not differ significantly from the expected 1:1 ratio. Gene order was determined by minimizing the number of double recombinants between loci and confirmed by the maximum likelihood analysis (BISHOP 1985). *Erbb*, the most proximal marker in the cross, was used as the anchor locus, and the other loci were placed distal to *Erbb* as shown in Figure 2. The distance between loci was calculated as follows: *Erbb*—3.5 ± 1.5 cM—*Rel*—12.5 ± 2.5 cM—*Pad-l*—6.3 ± 2.0 cM—[*Il-3, Csfgm*]—6.3 ± 2.0 cM—*Myhs*—4.9 ± 1.8 cM—*Trp53-1*—2.0 ± 1.2 cM—*Mov-9*—0.7 ± 0.7 cM—*Evi-2*—11.2 ± 2.6 cM—[*Cola-1, Hox-2*]—0.7 ± 0.7 cM—[*Erba, Erbb-2, Csfg*]—4.2 ± 1.7 cM—[*Int-4, Myla*]—3.5 ± 1.5 cM—*Pkca.*

There were several groups of loci in which no recombinants were observed, indicating a maximum map distance of 1.4 cM (upper 95% confidence limit) between the loci in each cluster. These clusters were 1) *Il-3* and *Csfgm*; 2); *Cola-1* and *Hox-2*; 3) *Erba, Erbb-2* and *Csfg*; and 4) *Myla* and *Int-4.*

TABLE 1

Listing of loci initially mapped in the interspecific backcross animals

Locus	Gene name	Probe	Enzyme	C57BL/6J fragment sizes (kb)	*M. spretus* fragment sizes (kb)[a]	Reference
Cola-1	α_1-*Collagen*	pI	*Taq*I	4.6, 3.3, 2.5, 2.1, 1.5, 1.0	4.8, 3.3, 2.5, 2.1, 1.5, 1.0	HARBERS *et al.* (1984)
Csfg	*Granulocyte colony-stimulating factor*	pBRG-4	*Taq*I	3.9	2.5	TSUCHIYA *et al.* (1986)
Csfgm	*Granulocyte-macrophage colony-stimulating factor*	pE1-11	*Pst*I	2.8	6.4	MIYATAKE *et al.* (1985)
Il-3	*Interleukin-3*	fpGV-IL12	*Msp*I	2.1	2.4, 1.4	FUNG *et al.* (1984), BUCHBERG *et al.* (1988)
Erba	*Avian erythroblastosis virus A* oncogene	v-ErbA	*Taq*I	4.4, 4.1, 1.5	2.3, 1.5	BUCHBERG *et al.* (1988)
Erbb	*Avian erythroblastosis virus B* oncogene	v-ErbB	*Bam*HI	9.3	11.0	BUCHBERG *et al.* (1988)
Erbb-2	*Neu* proto-oncogene	neuc(t)/sp6400	*Pst*I	4.0	4.4	BARGMANN, HUNG and WEINBERG (1986)
Evi-2	*Ectropic viral integration site-2*	p597.1	*Taq*I	2.1	1.7	BUCHBERG *et al.* (1988)
Hox-2	*Homeobox locus-2*	pMu1	*Msp*I	2.4	1.9, 0.5	JOYNER *et al.* (1985)
Int-4	*MMTV integration site-4*	pBG14	*Taq*I	4.4	6.8	H. ROELINK and R. NUSSE (personal communication)
Mov-9	*Moloney virus integration site-9*	pMov9-1-2	*Msp*I	3.5	1.9	CHUMAKOV *et al.* (1982)
Myhs	*Myosin heavy chain*	p32	*Taq*I	18.5, 12.2, 11.0, 6.0, 4.9, 4.5, 3.3, 2.5	18.5, 12,2, 11.0, 9.0, 3.3, 2.5	WEYDERT *et al.* (1983)
Myla	*Myosin light chain*	pMyla	*Taq*I	6.5, 2.3, 1.5, 1.0	4.8, 2.3, 1.5, 1.0	BARTON *et al.* (1988)
Pad-1	*MMTV LTR integration site*	pPad-1	*Taq*I	6.0	2.4	A. SONNENBERG (personal communication)
Pkca	*Protein kinase C α-chain*	pbPKC-α21	*Hin*dIII	13	9.3	PARKER *et al.* (1986)
Rel	*Reticuloendotheliosis virus* oncogene	v-rel	*Taq*I	10.0	4.7	BROWNELL *et al.* (1985)
Trp53-1	*Transforming protein 53*	p53-c19	*Bgl*I	18.0	5.8	BENCHIMOL *et al.* (1984)

[a] Underlined restriction fragment size indicates the segregating allele(s) that was typed in the analysis.

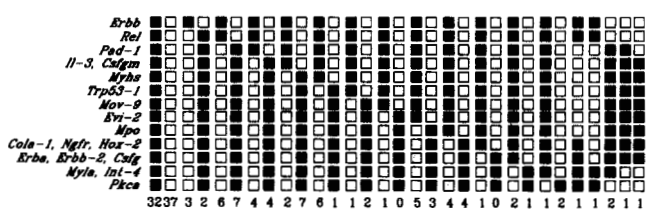

FIGURE 1.—Summary of the results of the interspecific backcross analysis. Genes mapped in the analysis are listed on the left. Each column represents the chromosome identified in the N2 progeny that was inherited from the [C57BL/6J × *M. spretus*] F_1 parent. The black boxes represent the presence of a C57BL/6J allele and the open boxes represent the presence of a *M. spretus* allele. The number of each type of chromosome observed in the interspecific backcross analysis is listed at the bottom.

Linkage conservation between human chromosome *5* and mouse chromosome *11*: *Il-3* and *Csfgm*, which map to mouse chromosome *11*, have been localized to human chromosome *5* (IHLE, SILVER and KOZAK 1987; HUEBNER *et al.* 1985). The genes *Pdgfr* and *Fms* are linked to *Il-3* and *Csfgm* on human chromosome *5* (YARDEN *et al.* 1986). We were interested in determining if the linkage of *Pdgfr* and/or *Fms* to *Il-3* and *Csfgm* was conserved between mouse and man. RFLPs were identified for *Pdgfr* and *Fms* (Table 2) and the segregation of *M. spretus* alleles was followed in the N2 backcross animals. There was no evidence of linkage of *Pdgfr* and *Fms* to any locus on chromosome *11* (data not shown). However, the results demonstrated that *Pdgfr* and *Fms* were closely linked (no recombinants in 86 N2 animals scored), and map to mouse chromosome *18* (HOGGAN *et al.* 1988). Close linkage of *Fms* and *Pdgfr* in the mouse is consistent with their close linkage in humans (ROBERTS *et al.* 1988).

Linkage conservation between human chromosome *17* and mouse chromosome *11*: Comparative mapping results demonstrated that mouse chromosome *11* contains an extensive region of homology to

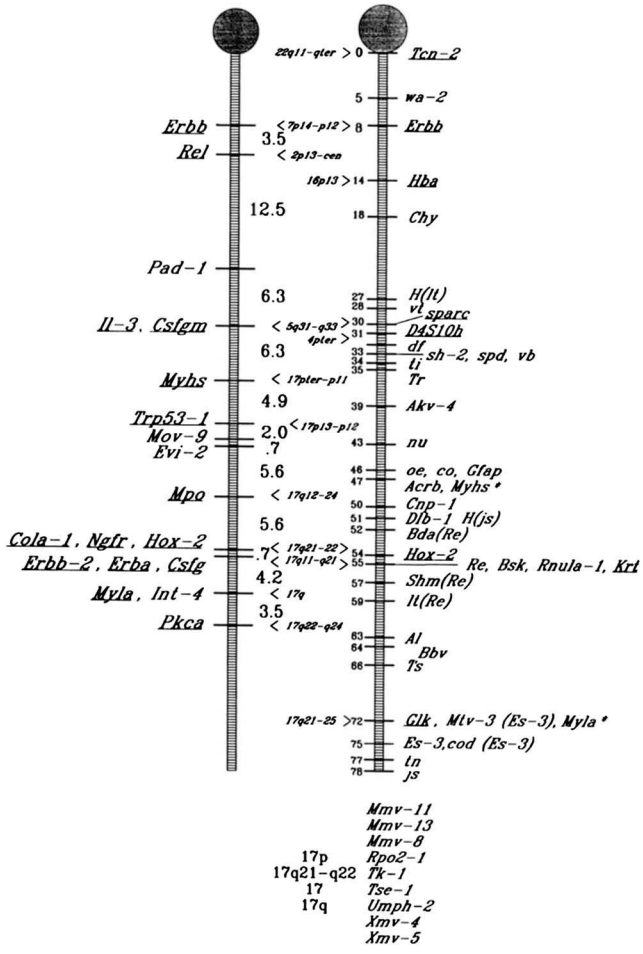

FIGURE 2.—Linkage map of mouse chromosome *11*. The chromosome on the right shows the 1988 linkage map of mouse chromosome *11* compiled by T. H. RODERICK, M. T. DAVISSON, A. L. HILLYARD and D. P. DOOLITTLE (personal communication). The loci with asterisks (*) indicate differences in map position as determined from this study (see DISCUSSION). The chromosome on the left is the linkage map of mouse chromosome *11* generated from our interspecific backcross analysis. The loci mapped in this study and their distance in cM from each neighboring locus are shown on the left chromosome. Located between the two chromosomes are the locations of the underlined loci on the human chromosome linkage map.

human chromosome *17* (reviewed in NADEAU and REINER 1989). We have been interested in determining the extent of this linkage conservation between mouse chromosome *11* and human chromosome *17*. *Ngfr* and *Mpo* have been localized to human chromosome *17* near *Hox-2* and *Erba* at band *q21* (HUEBNER *et al.* 1986; VAN TUINEN *et al.* 1987a; CHANG *et al.* 1987). *Ngfr* and *Mpo* have not been previously localized in the mouse.

RFLPs were determined for *Ngfr* and *Mpo* (Table 2). The segregation of *M. spretus* alleles was determined in the interspecific backcross progeny. The results of the segregation analysis revealed that *Ngfr* and *Mpo* are localized to mouse chromosome *11* and allowed for a placement of these genes on chromosome *11* (Figures 1 and 2). The mapping results place *Mpo* 5.6 ± 1.9 cM distal to *Evi-2* and 5.6 ± 1.9 cM proximal to *Cola-1*. *Ngfr* mapped to the gene cluster defined by *Cola-1* and *Hox-2*, with no recombinants among any of these three genes.

DISCUSSION

We have generated a multilocus linkage map of mouse chromosome *11*. This map covers over 70% of the chromosome [55.8 cM mapped out of a total length of 78 cM for mouse chromosome *11* (T. H. RODERICK, M. T. DAVISSON, A. L., HILLYARD and D. P. DOOLITTLE, personal communication)]. The density of markers in this cross was 0.34 loci/cM (19 loci mapped over a 55.8 cM distance, with the largest distance between two adjacent markers being 12.5 cM). Thus, we are quite confident of detecting most, if not all, double recombinants. A total of 69 single crossover events were detected among 144 informative interspecific backcross animals. Six double recombinants were observed (Figure 1), which is not significantly different ($P > 0.05$) from the expected number of 11 double recombinants.

Comparison to previously published mapping data: Several loci mapped in our analysis have previously been positioned on mouse chromosome *11*. *Hox-2* has been localized 1 cM proximal to *Rex* (*Re*) by the analysis of recombinant inbred and intraspecific backcross animals (HART *et al.* 1988). Our results using multilocus interspecific backcross analysis place *Hox-2*

TABLE 2

Listing of loci mapped in the interspecific backcross animals based on human-mouse homologies

Locus	Gene name	Probe	Enzyme	C57BL/6J fragment sizes (kb)	*M. spretus* fragment sizes (kb)[a]	Reference
Fms	*Feline sarcoma virus* oncogene (*Csfm receptor*)	341-pp1	*Msp*I	3.2	3.5	SOLA *et al.* (1986)
Mpo	*Myeloperoxidase*	pGM706	*Bam*HI	2.4	4.0	MORISHITA *et al.* (1987)
Ngfr	*Nerve growth factor receptor*	p5b	*Taq*I	6.8, 3.4, 1.8	6.9, 3.4, 1.8	BUCK *et al.* (1989)
Pdgfr	*Platelet-derived growth factor receptor*	pGR102	*Taq*I	7.1, 4.8, 1.5	5.6, 3.4, 1.5	YARDEN *et al.* (1986)

[a] Underlined restriction fragment size indicates the segregating allele(s) that was typed in the analysis.

in the same location (1 cM proximal to *Re*) using as the sole anchor locus, *Erbb*, which is 47 cM proximal to *Hox-2*. The results of the *Hox-2* mapping provide support for the utility and fidelity of using interspecific backcross analysis for linkage studies.

Myhs was previously placed on mouse chromosome *11*, 33 cM distal to *Hba*, by interspecific backcross analysis (ROBERT *et al.* 1985; WEYDERT *et al.* 1985); these results would place *Myhs* 1 cM distal to *cocked* (*co*) and *open eyelids* (*oe*) (Figure 2). However, our results place *Myhs* approximately 10 cM proximal to *co* and *oe* (Figure 2). The original mapping studies of *Myhs* used *hemoglobin α-chain* (*Hba*) and *esterase-3* (*Es-3*) as flanking markers; these two genes are 61 cM apart on chromosome *11*. The large distance separating these markers would preclude a precise localization of *Myhs* on chromosome *11*. Our multilocus linkage analysis, with a marker density of 0.34 loci/cM, allows for a more precise placement of *Myhs* on chromosome *11*. Similarly, we find a different map location for *Myla* from that previously published. *Myla* was originally placed 6.8 ± 3.3 cM proximal to *Es-3* using interspecific backcross analysis (ROBERT *et al.* 1985) and is placed 3 cM proximal to *Es-3* on the most recent mouse chromosome map (T. H. RODERICK, M. T. DAVISSON, A. L. HILLYARD and D. P. DOOLITTLE, personal communication). Although we did not include *Es-3* in our cross, our results would place *Myla* approximately 13 cM proximal to its previous location.

Clusters of genes on chromosome *11*: The interspecific backcross analysis reported here identified four clusters of closely linked genes (there were no recombinants out of 144 progeny analyzed, indicating a maximum map distance of 1.4 cM, 95% confidence interval). These clusters were: 1) *Il-3* and *Csfgm*; 2) *Cola-1*, *Ngfr* and *Hox-2*; 3) *Erba*, *Erbb-2* and *Csfg*; and 4) *Myla* and *Int-4*. The presence of gene clusters implies either close linkage or may result from small inversions in *M. spretus* chromosomes relative to C57BL/6J chromosomes, causing a suppression of recombination in these regions. The latter explanation seems unlikely for several reasons. First, the map position of *Hox-2* was accurately determined in the interspecific cross using an anchor locus, *Erbb*, that mapped 47 cM proximal to *Hox-2*. Second, *Csfgm* and *Il-3* are known to be closely linked molecularly in mouse; both loci are present on the same 230-kb restriction endonuclease fragment (BARLOW *et al.* 1987). Thus, the close genetic linkage of *Il-3* and *Csfgm* was not unexpected. Similarly, *Erbb-2* and *Erba* are frequently coamplified in human tumors (VAN DE VIJUER *et al.* 1987) and gene transfer experiments involving human chromosome *17* have demonstrated that *Ngfr*, *Cola-1* and *Hox-2* are cotransferred at a high frequency (XU *et al.* 1987), indicating that they are closely linked in humans.

Linkage conservation between human chromosome *5* and mouse chromosome *11*: A small conserved linkage group, defined by *Csfgm* and *Il-3*, has been identified between human chromosome *5q* and mouse chromosome *11* (BARLOW *et al.* 1987; BUCHBERG *et al.* 1988). Another locus, *sparc* (*osteonectin*), has also been mapped to both human chromosome *5q* and mouse chromosome *11*, showing linkage with *Csfgm* and *Il-3* in both mouse and human (MASON *et al.* 1986; SWAROOP, HOGAN and FRANCKE 1988). This finding defines a third member of the conserved linkage group. However, it is evident that other loci, such as *Pdgfr*, *Csfm* and *Fms*, which also map to human chromosome *5q*, are not located on mouse chromosome *11*. Two of these genes, *Pdgfr* and *Fms*, map to mouse chromosome *18*, defining yet another conserved linkage group between mouse and human (HOGGAN *et al.* 1988; this study). The chromosomal location of *Csfm* is presently unknown; however, interspecific backcross analysis indicated that it does not map to mouse chromosome *11* or mouse chromosome *18* (BUCHBERG *et al.* 1988; this study). The long arm of human chromosome *5* is often deleted in human myeloid disease, macrocytic anemia and acute nonlymphocytic leukemia ($5q^-$ syndrome) (reviewed in BUNN 1986). The genes *Il-3*, *Csfgm*, *Fms* and *Csfm* are almost always deleted in this syndrome (LEBEAU *et al.* 1986). However, to date no deletion or rearrangement of mouse chromosome *11* has been associated with murine myeloid disease. The absence of a comparable $5q^-$ syndrome in mice may reflect the dispersion of the gene(s) involved in the $5q^-$ syndrome in mice. There are several other genes that map to human chromosome *5q*, including the monocyte cell surface antigen, *CD14*, *β-adrenergic receptor* (*ADRBR*) and *acidic fibroblast growth factor* (*endothelial growth factor, FGFA*) (GOYERT *et al.* 1988; KOBILKA *et al.* 1987; MODI, JAYE and O'BRIEN 1987). It will be of interest to determine the chromosomal localization of these genes in mouse to determine the extent of the linkage conservation with mouse chromosome *11* and *18*.

Linkage conservation between human chromosome *17* and mouse chromosome *11*: A much larger conserved region is observed when the distal portion of mouse chromosome *11* is compared to human chromosome *17*. To date, every locus on human chromosome *17* that has been mapped in the mouse has been localized to mouse chromosome *11*, distal to *Myhs*. The map distance between *Myhs* and *galactokinase* (*Glk*), the most proximal and distal marker on mouse chromosome *11* showing synteny with human chromosome *17*, is 36 cM (Figure 2). This conserved region represents one of the largest conserved seg-

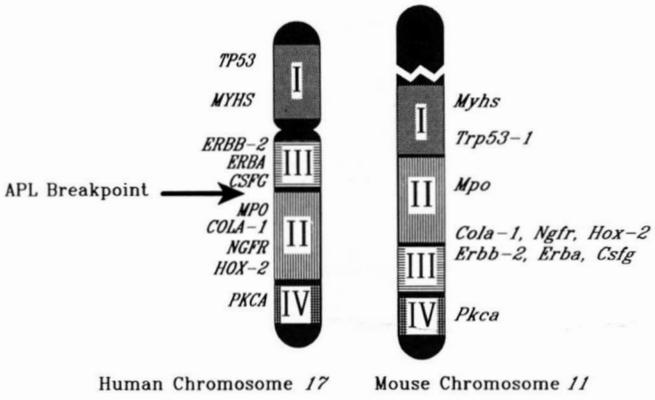

FIGURE 3.—Comparison of mouse chromosome *11* and human chromosome *17*. Mouse chromosome *11* (right) represents the region of mouse chromosome *11* that is homologous to human chromosome *17* (left). Mouse chromosome *11* shows the relative position of loci that have been localized on human chromosome *17*. The regional location of those loci are depicted on human chromosome *17*. The regions of synteny are shown in different shadings and labeled with Roman numerals (I–IV). The location of the acute promyelocytic breakpoint (APL) is shown.

ments yet identified between mouse and human (NADEAU and TAYLOR 1984; reviewed in NADEAU and REINER 1989).

Figure 3 shows a comparison of gene locations on mouse chromosome *11* with respect to their locations on human chromosome *17*. The loci *Myhs* and *Trp53-1* are located 5 cM apart on mouse chromosome *11* and are both located on the short arm of human chromosome *17* (*MYHS* and *TP53*, respectively; region I in Figure 3). One would predict that the gene encoding the large subunit of RNA polymerase II, *RPII* (*Rpo2-1*, locus designation in mice), which has been mapped to the short arm of human chromosome *17* (CANNIZZARO *et al.* 1986) and to mouse chromosome *11* by somatic cell hybrid analysis (PRAVTCHEVA *et al.* 1986), would be located in the region defined by *Myhs* and *Trp53-1* in the mouse. The next more distal gene on mouse chromosome *11* whose location is known in humans is *MPO* (region II in Figure 3). *MPO* is located on the long arm of human chromosome *17* at band *q21-24* (VAN TUINEN *et al.* 1987a; CHANG *et al.* 1987). Since *TP53-1* is located at the telomere of the short arm of human chromosome *17* and *MYHS* is located toward the centromere of the short arm of human chromosome *17* (ISOBE *et al.* 1986; MCBRIDE, MERRY and GIVOL 1986; LEINWAND *et al.* 1983), it is evident that at least one inversion occurred to account for the inverted order of *Myhs*, *Trp53-1* and *Mpo* between mouse and human, assuming gene order is reliable in both species.

A convenient physical marker for the long arm of human chromosome *17* is the translocation breakpoint at band *17q12* that is seen in all patients with acute promyelocytic leukemia (APL) (KANEKO and SAKURAI 1977; ROWLEY, GOLOMB and DOUGHERTY 1977; LARSON *et al.* 1984). Two gene clusters, defined by 1) *Ngfr, Hox-2* and *Cola-1* and 2) *Erba, Erbb-2* and *Csfg* (regions II and III, respectively, in Figure 3), which map 0.7 ± 0.7 cM apart on mouse chromosome *11*, have been mapped to the long arm of human chromosome *17*. The two clusters map to either side of the APL breakpoint (XU *et al.* 1987). The location of *MPO* is distal to the APL breakpoint but proximal to both these closely linked clusters on mouse chromosome *11*, indicating the presence of at least one rearrangement in this interval between the two chromosomes. *Pkca* which maps distal on mouse chromosome *11* (region IV) (YANG-FENG, ULLRICH and FRANCKE 1987), also maps distal to the APL breakpoint on human chromosome *17* (COUSSENS *et al.* 1986). These observations suggest that human chromosome *17* can be generated from mouse chromosome *11* by a rearrangement in region I and the insertion of region III between region I and region II (Figure 3).

Identification of murine homologs of genes involved in human disease: It has been recently reported that rearrangements in *MPO* are detected in two of four cases examined of APL translocation chromosomes, suggesting that *MPO* might be causally associated with APL (WEIL *et al.* 1988). However, a causal association between these *MPO* rearrangements and APL has not yet been firmly established. The mapping results presented here suggest that the murine homolog of the human chromosome *17* APL breakpoint region might be located between the two closely linked gene clusters defined by *COLA-1-NGFR-HOX-2* and *ERBB-2-ERBA-CSFG*, if this region is conserved between mouse and man. These clusters are 0.7 ± 0.7 cM apart, which roughly correlates to about 0.8 to 1.6 million base pairs (Mbp) [assuming the total length of the mouse genome is 1600 cM (RODERICK and DAVISSON 1981) and there is 3×10^3 Mbp in the mouse genome]. Alternatively, the observation that the linear order of genes is not conserved between mouse chromosome *11* and human chromosome *17* makes it difficult to predict the exact location of the murine homolog of the human chromosome *17* APL breakpoint region. In this regard, preliminary *in situ* hybridization results using a human homolog of *Evi-2*, a common viral integration site in murine myeloid tumors, maps *Evi-2* to human chromosome *17q11-q12*, in the region near the APL breakpoint (M. M. LEBEAU, personal communication). This localization makes *Evi-2* another potential candidate for involvement in the translocation breakpoint. *Evi-2* maps approximately 11 cM proximal to *Cola-1-Ngfr-Hox-2* on murine chromosome *11* (Figure 2). If *Evi-2* is the mouse counterpart of the human chromosome *17* region causally associated with human APL, this would suggest the presence of yet another chromo-

some rearrangement separating mouse chromosome *11* and human chromosome *17*. We are currently pursuing the precise localization of *Evi-2* with respect to the translocation breakpoint to determine if it is the gene that is causally associated with human APL.

The gene defect involved in von Recklinghausen neurofibromatosis (vRNF) has also been localized to the long arm of human chromosome *17*, at or near bands *q11-12* (BARKER *et al.* 1987; SEIZINGER *et al.* 1987; VAN TUINEN *et al.* 1987b). The localization of *vRNF* makes it likely that the human homolog of *Evi-2* would be closely linked and might serve as a useful molecular marker to gain access to the *vRNF* locus.

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