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Genetic map of seven polymorphic markers comprising a single linkage group on rat Chromosome 5

Ellen A. Goldmuntz, Elaine F. Remmers, Hongbin Zha, Peter Mathern, Ying Du, Leslie J. Crofford, Ronald L. Wilder

Arthritis and Rheumatism Branch, Building 10, Room 9N228, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA

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Abstract. Seven polymorphic markers comprising a single linkage group were assigned to rat Chromosome (Chr) 5 by linkage analysis of the progeny of an F_2 intercross of Fischer (F344/N) and Lewis (LEW/N) inbred rats. Three genes, α-L-fucosidase 1 (*FUCA1*), mitochondrial superoxide dismutase (*SOD2*), and glucose transporter (*GLUT1*), were mapped by restriction fragment length polymorphism (RFLP) analysis. Two genes, glucose transporter (*GTG3*) and elastase II (*ELAII*), one pseudogene for α tubulin (*TUBAPS*), and one sequence related to the 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase gene (*PFKFBP1*-related sequence) were mapped by simple sequence repeat (SSR) polymorphism analysis. The loci are in the following order: *SOD2, GTG3/GLUT1, FUCA1, ELAII/PFKFBP1*-related sequence, and *TUBAPS*. This linkage group covered 68.3 cM of rat Chr 5. The SSR markers were highly polymorphic in 13 inbred rat strains (SHR/N, WKY/N, MNR/N, MR/N, LOU/MN, BN/SsN, BUF/N, WBB1/N, WBB2/N, ACI/N, LER/N, F344/N, and LEW/N). These markers, located on rat Chr 5, will be useful in genetic studies of inbred rats.

Introduction

The rat is widely used as an experimental animal model for many human diseases including such diverse conditions as inflammatory arthritis and other autoimmune diseases, hypertension, diabetes, obesity, environmentally induced malignancy, drug addition, and other behavioral abnormalities. Many of these multifactorial conditions appear to have a genetic component that is difficult to evaluate in humans. Inbred animals, however, provide a unique opportunity to study this type of complex disease because the contributing genetic and environmental factors can be manipulated independently. To identify the genetic loci involved in the pathogenesis of multifactorial diseases in the rat, it is necessary to have detailed genetic maps. Although extensive genetic linkage maps are available for mouse and human, only recently have rudimentary genetic linkage maps for the rat been published (Serikawa et al. 1992; Hilbert et al. 1991; Zha et al. 1993; Remmers et al. 1992; Remmers et al. 1993). The continued expansion of the rat genetic map with highly polymorphic DNA markers will permit the study of the genetic contribution to complex multifactorial and multigenic diseases in many inbred strains of rats.

The Lewis (LEW) and Fischer (F344) strains are of particular interest because they differ in their susceptibility to a wide variety of autoimmune, inflammatory diseases that serve as models for human diseases such as rheumatoid arthritis (Wilder et al. 1982; Griffiths and DeWitt 1984; Sano et al. 1990), multiple sclerosis (Levine and Wenk, 1965), and autoimmune uveitis (Caspi et al. 1992). To identify the genetic loci responsible for these phenotypes, a genetic map applicable to these two strains is required. The identification of the involved loci in these rats may further the understanding of the genetic components of susceptibility to autoimmune disease in humans.

Using the progeny of an F_2 intercross of F344/N and LEW/N rats, we now report a genetic linkage map of seven polymorphic DNA markers assigned to rat Chr 5. These seven markers formed a single linkage group covering 68.3 cM.

Materials and methods

Animal breeding and DNA extraction

F344/N and LEW/N rats were obtained from Harlan-Sprague-Dawley (Indianapolis, Ind.). Generation of the F344/N × LEW/N F_2

Correspondence to: E.A. Goldmuntz

intercross population and DNA extraction have been described previously (Remmers et al. 1992).

Restriction fragment length polymorphism analysis

Genomic DNA samples (10 μg) from parental F344/N and LEW/N animals and an F_1 animal were digested with each of 12 restriction endonucleases. The fragments were separated by electrophoresis on 1% agarose gels, transferred to nylon membranes (Nytran, Schleicher and Schuell, Keene, N.H.), and hybridized to ^{32}P-labeled, random-primed inserts purified from the plasmid DNAs obtained from the American Type Tissue Collection as described in Table 1. All hybridizations were performed at 65°C. The membranes were washed in 0.1 × SSC, 0.1% SDS at 60°C after hybridization with the *SOD2* and *GLUT1* probes. The wash temperature was 55°C after hybridization with the *FUCA1* probe. Polymorphic fragment sizes were estimated by comparison with molecular weight standards run on the same agarose gel with a computer program, DNAFIT (Oerter et al. 1990).

Simple sequence repeat polymorphisms

Simple sequence repeats (SSRs) were identified in rat DNA sequences from GenBank with the FINDPATTERNS program of the Genetics Computer Group Sequence Analysis Software Package (Devereux et al. 1984). Primer pairs (listed in Table 1) flanking the repeats were designed, and genomic DNA (1 μg) from F344/N and LEW/N parental animals and an F_1 heterozygote was amplified under polymerase chain reaction (PCR) conditions described previously (Remmers et al. 1992).

The denatured PCR products were separated on 8% polyacrylamide, 8 M urea sequencing gels and visualized by autoradiography. Amplified fragment sizes were estimated by comparison with labeled molecular weight standards run on the same gel. For all of the markers, alleles were identified by the amplification of different-sized bands from parental genomic DNA. Both bands were amplified in DNA from heterozygous animals.

Linkage analysis

Genotypes of 40 F_2 F344/N × LEW/N intercross progeny were determined for each of the polymorphic markers. The segregation of the alleles in the F_2 intercross generation was analyzed on a VAX 8650 computer with the computer program package MAPMAKER Version 1.9 (Lander et al. 1987), which performs multi-point linkage analysis and constructs linkage maps based on maximum likelihood calculations. Standard errors for the distances between pairs of markers were calculated according to Green's algorithm (Green 1981).

Detection of polymorphisms in other inbred rat strains

The SSRs were amplified with template DNA from 11 other inbred rat strains (BN/SsN, LER/N, ACI/N, BUF/N, LOU/MN, MR/N, MNR/N, SHR/N, WKY/N, WBB1/N, WBB2/N) obtained from the Genetic Resource Section of the Veterinary Resources Program of the National Center for Research Resources at the National Institutes of Health. DNA isolation, PCR amplification and fragment size determination were performed as described above.

Results

Restriction fragment length polymorphisms

SOD2 (superoxide dismutase, mitochondrial) and *FUCA1* (α-L-fucosidase 1) RFLPs were detected in *Bam*HI-digested DNAs with the probes described in Table 1. The F344/N and LEW/N allele sizes are listed in Table 1. A *GLUT1* (glucose transporter) RFLP was detected in *Msp*I-digested DNAs with the probe described in Table 1. The F344/N and LEW/N allele sizes are also listed in Table 1. The human locus names (McAlpine et al. 1991) have been used for the homologous rat loci whenever possible. The F344/N, LEW/N, and heterozygous band patterns are shown in Fig. 1.

Simple sequence repeat polymorphisms

Polymorphic SSRs were identified in sequences encoding two genes, *GTG3* (glucose transporter) and

Table 1. Probes and primers used for polymorphism analysis in F344/N and LEW/N rats.

Restriction fragment length polymorphisms

Locus	Probe information	Enzyme	F344 allele	LEW allele
FUCA1	AF3 (ATCC# 57542) contains human α fucosidase, 1.06-kb insert, *Eco*RI ends	*Bam*HI	3.7 kb	3.5 kb
SOD2	phMnSOD4 (ATCC# 59946) contains human mitochondrial superoxide dismutase, 0.83-kb insert, *Eco*RI ends	*Bam*HI	8.0 kb	10.1 kb
GLUT1	pSGT (ATCC# 59630) contains human glucose transporter, 2.47-kb insert, *Hae*III ends	*Msp*I	2.2 kb	2.0 kb

Simple sequence repeat polymorphisms

LOCUS	GENBANK ref. accession #	Sense primer Anti-sense primer	F344 allele	LEW allele
GTG3	ratgtg3.ro M22063, J04220	5′TATGACAGATAGCCCAGAAGCC3′ 5′CACCGTGAAGATGATGAAGACG3′	233 bp	235 bp
ELAII	ratelaii1.ro L00118, J00731	5′ACCAAGACAGCAAACATCAACC3′ 5′CGAAGAAAAATACCAGACCAGC3′	258 bp	281 bp
PFKFBP1-related	pfkfbp1.ro M26215	5′AGAGTGCATCTCTGACCTCTCC3′ 5′CCTGTGGACGCCACATAAAAGC3′	178 bp	177 bp
TUBAPS	rattubaps.ro J00799	5′ATGGTGAAATGTGACCCTCGCC3′ 5′TCAGCAATGGCTGTGGTGTTCC3′	370 bp	367 bp

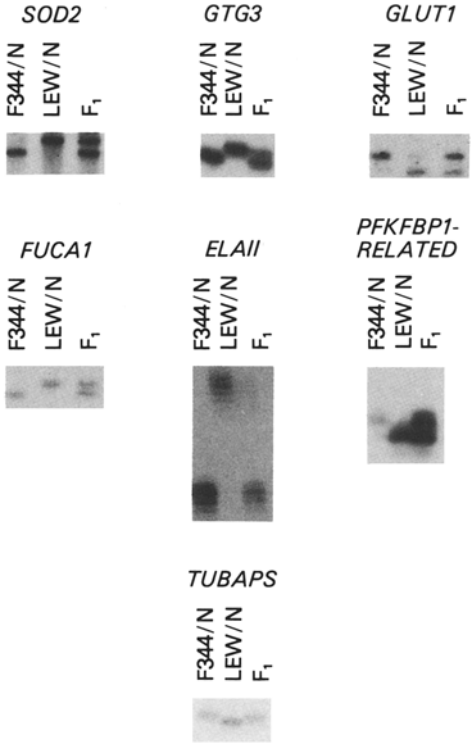

Fig. 1. Homozygous F344/N, homozygous LEW/N, and heterozygous F_1 patterns of rat Chr 5 markers. Marker locus names are above each panel. Estimates of allele sizes are listed in Table 1.

ELAII (elastase II), one pseudogene *TUBAPS* (α tubulin pseudogene), and one sequence related to the 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase gene, *PFKFBP1*-related sequence. The sequences of the primers used to amplify the SSR polymorphisms, the allele size estimates, and the GenBank reference information for each sequence are listed in Table 1. The F344/N, LEW/N, and F_1 heterozygote band patterns are shown in Fig. 1.

Table 2. Genotypes of Chr 5 linkage group markers in the F344/N × LEW/N F_2 progeny.

Number of rats	*SOD2*	*GTG3* and *GLUT1*	*FUCA1*	*ELAII* and *PFKFBP1*-related	*TUBAPS*
5	H[a]	H	H	H	H
3	L	L	L	L	L
2	F	F	F	F	F
1	F	F	F	F	H
1	F	F	F	H	H
1	H	H	H	F	F
1	F	F	H	H	—
1	F	F	H	H	H
2	L	L	H	H	H
1	H	H	L	L	L
1	F	H	H	H	H
4	L	H	H	H	H
1	H	L	L	L	L
1	F	F	H	F	F
1	H	F	F	L	L
1	H	F	L	L	L
1	H	F	H	L	L
1	L	H	H	H	F
1	H	H	F	H	H
1	H	H	L	H	H
2	L	H	H	F	F
1	H	F	F	H	H
1	H	F	H	H	H
3	H	L	H	H	H
1	L	H	F	F	F
1	F	H	L	L	L

[a] F = homozygous for F344/N allele; L = homozygous for LEW/N allele; H = heterozygous (both F344/N and LEW/N alleles); and — = not determined.

Linkage analysis

The genotypes of 40 F344/N × LEW/N F_2 intercross progeny were determined for these seven polymorphic markers and are listed in Table 2. The frequency of the genotypes did not differ from that predicted by Mendelian genetics for any marker (χ^2 = 0.10–0.81, 2 degrees of freedom, p = 0.67–0.95). Analysis of the allele segregation with the MAPMAKER computer package (Lander et al. 1987) indicated that they were members of a single linkage group covering 68.3 cM. Genetic distances were derived directly from the recombination frequency. The most probable linkage map is shown in Fig. 2. Support ratios favoring the stated map over a map with each pair of markers reversed are also shown in Fig. 2. The recombination

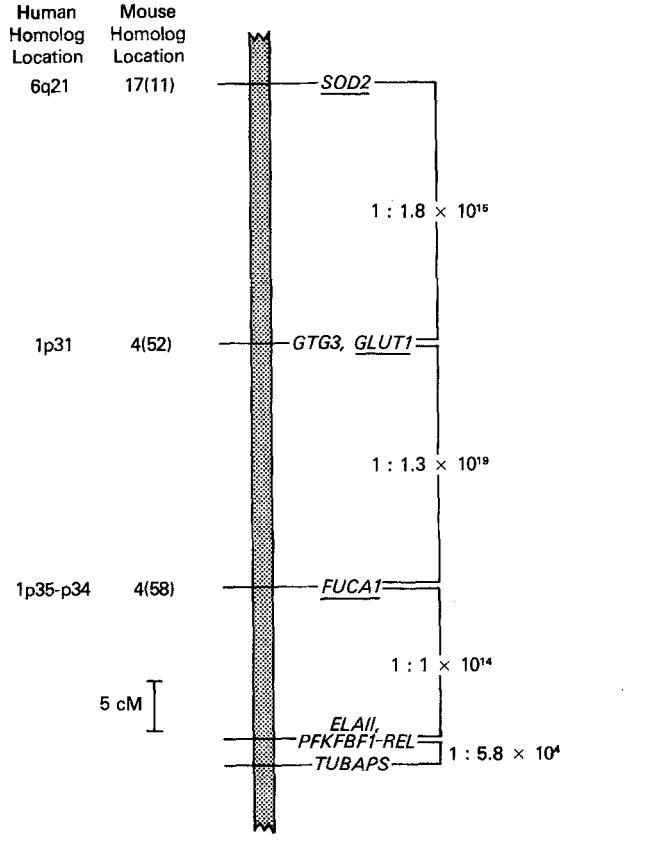

Fig. 2. Genetic linkage map of rat Chr 5. The thick shaded bar represents the rat Chr 5 linkage group. Locations of the centromere and the termini are not implied or indicated. Support ratios favoring the depicted order over a map with the order of each pair of markers reversed are listed to the right of the two loci. The genetic distances between the markers are derived directly from the percentage recombination. For the underlined loci, the map locations of the human and/or mouse homologs are listed to the left of the bar. For the mouse homologs, the distance in centimorgans from the centromere is indicated in parentheses when known.

Table 3. Recombination fraction between paris of rat Chr 5 markers.

Pair of loci	Meioses	Recombination fraction (±SE)
SOD2–GTG3	80	0.262 (±0.049)
GTG3–GLUT1	78	0
GLUT1–FUCA1	78	0.243 (±0.049)
FUCA1–ELAII	78	0.152 (±0.041)
ELAII–PFKFBP1- related	78	0
PFKFBP1- related–*TUBAPS*	78	0.026 (±0.018)

fraction between pairs of markers and their standard errors are listed in Table 3.

Analysis of SSR markers in other inbred rat strains

To determine the extent of polymorphism and the usefulness of these SSR polymorphisms in crosses of other inbred rat strains, we amplified genomic DNA from animals of 11 additional inbred rat strains with the primers for the four SSR polymorphisms. Two to five alleles were detected for each marker. The distribution of these alleles is shown in Table 4.

Discussion

We have reported here seven polymorphic DNA markers that form a single linkage group covering 68.3 cM. Two of the markers, *GLUT1* and *GTG3*, have been previously assigned to rat Chr 5 by somatic cell hybrid analysis (Serikawa et al. 1992; Szpirer et al. 1990), permitting the assignment of the entire linkage group to this chromosome. Both *GTG3* and *GLUT1* are markers for glucose transporter genes that are defined by different techniques. It is unclear from our analysis whether they are markers for the same gene or whether they are markers for related genes that are located close to one another on Chr 5.

An analysis of our genotyping data suggests that there is positive interference in the rat. Although the haplotypes for the maternally and paternally derived chromosomes must be inferred for F_2 intercross data, our data demonstrate a shortage of nonrecombinant and multiply recombinant chromosomes when compared with expected numbers if recombination events occurred at random (that is, no interference). Although based on small numbers and an assumption concerning haplotypes, these data suggest that positive interference occurs in the rat as in the mouse and many other eukaryotes.

The linkage group reported here is the largest Chr 5 linkage group of polymorphic DNA markers reported to date and includes five markers not previously mapped. On the basis of an estimated size of 2400 cM for the entire rat genome (Jacob et al. 1991) and assuming that the genetic length of the chromosome is proportional to its physical length, this linkage group covers approximately 48% of rat Chr 5. Serikawa and colleagues (1992) reported two linkage groups, one comprised of two markers and one comprised of five markers and two unlinked markers assigned to rat Chr 5. Of the eight markers, only four were defined by SSR analysis. We were unable to detect DNA polymorphisms between F344/N and LEW/N rats with the primers for *A2UG*, *PND*, and *A8* described by Serikawa and colleagues (1992). The classic rat linkage group II, which consists of 10 loci as depicted by Hedrich (1990), has also been assigned to rat Chr 5. Unfortunately, because there is insufficient overlap between these three maps, it is not possible to orient them relative to one another and make direct comparisons concerning map order and map distances.

We have compiled a table (Table 5) of the majority of loci mapped to rat Chr 5 and the human and mouse homologues when identified with their respective map locations. This comparison reveals clear conservation of synteny between rat Chr 5 and mouse Chr 4. Regions of human Chr 9 and human Chr 1 also display conservation of synteny with rat Chr 5. From these limited data, it appears that rat Chr 5 is more closely related to mouse Chr 4 than to either of the two human chromosomes discussed above.

To increase the usefulness of the SSR markers, we analyzed the genomic DNA from 11 additional inbred rat strains. We found that these markers were highly polymorphic with two to five alleles for each marker, suggestive that the SSR makers will be useful in the genetic analysis of crosses between other inbred rat

Table 4. Allele distribution of four polymorphic loci in 13 inbred rat strains.

Locus	Allele size (bp)	Rat strains
GTG3	233	F344/N, BN/SsN, BUF/N, WBB1/N, ACI/N
	235	LEW/N, LOU/MN, MNR/N, WBB2/N, MR/N, LER/N, SHR/N, WKY/N
ELAII	256	SHR/N
	258	WKY/N, ACI/N, MNR/N, WBB1/N, WBB2/N, MR/N, BN/SsN, F344/N
	280	LOU/MN
	281	LEW/N, LER/N
	283	BUF/N
PFKFBP1-related *SEQUENCE*	177	LER/N, LOU/MN, BUF/N, LEW/N
	178	MNR/N, F344/N, WBB1/N, WBB2/N, MR/N, SHR/N, WKY/N
	179	BN/SsN
TUBAPS	367	LER/N, SHR/N, WKY/N, MR/N, WBB1/N, MNR/N, BUF/N, BN/SsN, LEW/N
	370	ACI/N, WBB2/N, F344/N, LOU/MN

Table 5. Comparative map information for loci mapped to rat Chr 5.[a]

Rat locus	Description	Human locus	Human chromosome	Mouse locus	Mouse chromosome (cM)
ACO1	Aconitase	ACO1	9p22-q32	*Aco-1*	4 (22)
ALDOB	Aldolase B, fructose bisphosphatase	ALDOB	9q21.3-q22.2		
GGTB2	Glycoprotein 4-β galactosyl transferase 2	GGTB2	9p21-p13	*Ggtb*	4 (19)
IFNA	Interferon α	IFNA	9p22	*Ifa*	4 (39)
IFNB	Interferon β	IFNB	9p22	*Ifb*	4 (39)
ORM	Orosomucoid	ORM1, 2	9q31-qter	*Orm-1,-2*	4 (31)
AK2	Adenylate kinase 2	AK2	1p34	*Ak-2*	4
ENO1	Enolase 1	ENO1	1pter-p36.13	*Eno-1*	4 (73)
FUCA1	α-L-fucosidase 1	FUCA1	1p35-p34	*Fuca*	4 (58)
GDH	Glucose dehydrogenase	GDH	1p36		
GLUT1	Glucose transporter	GLUT1, 5	1p31	*Glut-1*	4 (52)
LCK1	Lymphocyte-specific protein tyrosine kinase	LCK	1p35-p32	*Lck*	4 (54)
MYCL	Avian myelocytomatosis viral oncogene homolog 1	MYCL1	1p32	*Lmyc-1*	4
PGD	Phosphogluconate dehydrogenase	PGD	1p36.3-p36.13	*Pgd*	4 (65)
PGM1	Phosphoglucomutase 1	PGM1	1p22.1	*Pgm-2*	4 (42)
PND	Pronatriodilatin	PND	1p36	*Pnd*	4 (66)
MOS	Moloney murine sarcoma viral oncogene	MOS	8q11	*Mos*	4 (6)
SOD2	Superoxide dismutase, mitochondrial	SOD2	6q21	*Sod-2*	17 (11)
AN	Anemia			*an*	4 (29)
B	Brown coat color (chocolate)			*b*	4 (35)
D4RP1	DNA segment from MMU4 (Roswell Park)			*Cyp4a*	4 (49)
DSI1	Moloney murine leukemia virus integration site			*Dsi-1*	4 (63)
FA	Fatty			*db*	4 (47)
HD	Hypodactyly			*Hd*	6 (28)
MUP	Major urinary protein			*Mup-1*	4 (29)
SAI1	Transformation suppressor				4
A2UG	α-2U globulin				
CU1	Curly				
D5G1	DNA segment from RN05 (Goteborg)				
IN	Incisorless				
S	Silver				
PBPC1	Prostatic binding protein C1				
PBPC2	Prostatic binding protein C2				
PBPC3	Prostatic binding protein C3				
SH	Shaggy				
ELAII	Elastase II				
TUBAPS	Tubulin pseudogene				
AHD2	Aldehyde dehydrogenase-2				

[a] Mapping information for rat genes, other than those reported here, was obtained from Serikawa and colleagues (1992), Levan and colleagues (1991), and Truett and colleagues (1991). The human locus and chromosome indicate the name and chromosomal location of the human homolog of the rat locus when known. The mouse locus and chromosome (cM) indicates the name and chromosomal location of the mouse homolog of the rat locus when known. The distance in cM from the centromere of the mouse locus is shown in parentheses. The information for mouse and human gene mapping was obtained from GBASE (1992), HGM 11 (McAlpine et al. 1991; Davisson et al. 1991), and Nadeau and colleagues (1992).

strains. They will also be useful for genetic monitoring of inbred rat strains.

The expansion of the genetic map of rat Chr 5 will be very useful in the dissection of the genetic components of multifactorial diseases. Several interesting phenotypes have been assigned to rat Chr 5, but none of the genes responsible have been identified. The rat obesity gene, fatty (*fa*), has been assigned to rat Chr 5 (Truett et al. 1991). The fatty mutation causes adiposity, hyperphagia, hyperinsulinemia, hyperlipemia, and multiple endocrine abnormalities and is one model for human obesity and diabetes. Nonrandom cytogenetic abnormalities in rat Chr 5, including complete loss of the chromosome, breakage, or translocation, have been identified in cell lines and primary tumor cells isolated from rats with hereditary renal cell carcinoma, a model for human hereditary renal cell carcinoma (Funaki et al. 1991). In vitro studies with somatic cell hybrids have localized a gene or a group of genes that control anchorage dependence and cell growth to the q22-23 portion of rat Chr 5 (Islam et al. 1989; Lewalle et al. 1991). The eventual identification of the loci responsible for these phenotypes will be possible with the continued expansion of the rat genetic map for Chr 5. The identification of these loci in rats may contribute to the identification of genes causing similar diseases in humans.

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References

Caspi, R.R., Chan, C.-C., Fujino, Y., Oddo, S., Najafian, F., Bahmanyar, S., Heremans, H., Wilder, R.L., Wiggert, B. (1992). Genetic factors in susceptibility and resistance to experimental autoimmune uveoretinitis. Curr. Eye Res. 11 (Suppl), 81–86.

Davisson, M.T., Lalley, P.A., Peters, J., Doolittle, D.P., Hillyard, A.L., Searle, A.G. (1991). Report of the comparative committee for human, mouse and other rodents. Cytogenet. Cell Genet. 58, 1152–1189.

Devereux, J., Haeberli, P., Smithies, O. (1984). A comprehensive set of sequence analysis programs for the VAX. Nucleic Acids Res. 12, 387–395.

Funaki, K., Everitt, J., Oshimura, M., Freed, J.J., Knudson, A.G. Jr., Walker, C. (1991). Hereditary renal cell carcinoma in the rat associated with nonrandom loss of chromosomes 5 and 6. Cancer Res. 51, 4415–4422.

GBASE (1992). The genomic database of the mouse maintained at The Jackson Laboratory by D.P. Doolittle, A.L. Hillyard, L.J. Maltais, J.N. Guidi, M.T. Davisson, T.H. Roderick.

Green, E. (1981). Linkage, recombination and mapping. In *Genetics and Probability in Animal Breeding Experiments,* E. Green, ed. (New York: Macmillan), pp. 77–113.

Griffiths, M.M., DeWitt, C.W. (1984). Genetic control of collagen-induced arthritis in rats: the immune response to type II collagen among susceptible and resistant strains and evidence for multiple gene control. J. Immunol. 132, 2830–2836.

Hedrich, H.J. (1990). Mutant genes and polymorphic loci of the laboratory rat. In *Genetic Monitoring of Inbred Strains of Rats,* H.J. Hedrich, ed. (Stuttgart: Gustav Fischer Verlag), pp. 289–409.

Hilbert, P., Lindpaintner, K., Beckmann, J.S., Serikawa, T., Soubrier, F., Dubay, C., Cartwright, P., De Gouyon, B., Julier, C., Takahasi, S., Vincent, M., Ganten, D., Georges, M., Lathrop, G.M. (1991). Chromosomal mapping of two genetic loci associated with blood-pressure regulation in hereditary hypertensive rats. Nature 353, 521–529.

Islam, M.Q., Szpirer, J., Szpirer, C., Islam, K., Dasncy, J.F., Levan, G. (1989). A gene for the suppression of anchorage independence is located in rat chromosome 5 bands q22-23, and the rat α-interferon locus maps at the same region. J. Cell Sci. 92, 147–162.

Jacob, H.J., Lindpaintner, K., Lincoln, S.E., Kusumi, K., Bunker, R.K., Mao, Y.-P., Ganten, D., Dzau, V.J., Lander, E.S. (1991). Genetic mapping of a gene causing hypertension in the stroke-prone spontaneously hypertensive rat. Cell 67, 213–224.

Lander, E.S., Green, P., Abrahamson, J., Barlow, A., Daly, M.J., Lincoln, S.E., Newburg, L. (1987). MAPMAKER: An interactive computer package for constructing primary genetic linkage maps of experimental and natural populations. Genomics 1, 174–181.

Levan, G., Szpirer, J., Szpirer, C., Klinga, K., Hanson, C., Islam, M.Q. (1991). The gene map of the Norway rat (*Rattus norvegicus*) and comparative mapping with mouse and man. Genomics 10, 699–718.

Levine, S., Wenk, E.J. (1965). Induction of experimental allergic encephalomyelitis in rats without the aid of adjuvant. Ann. N.Y. Acad. Sci. 122, 209–225.

Lewalle, J.M., Szpirer, C., Szpirer, J., Munaut, C., Foidart, J.M. (1991). Rat chromosome 5 (q22-23) contains elements that control cell morphology and interactions with the extracellular matrix: a study of normal fibroblast × malignant hepatoma cell hybrids. Exp. Cell Res. 196, 164–171.

McAlpine, P.J., Shows, T.B., Boucheix, C., Huebner, M., Anderson, W.A. (1991). The 1991 catalog of mapped genes and report of the nomenclature committee. Cytogenet. Cell Genet. 58, 5–102.

Nadeau, J.H., Davisson, M.T., Doolittle, D.P., Grant, P., Hillyard, A.L., Kosowsky, M.R., Roderick, T.H. (1992). Comparative map for mice and humans. Mammalian Genome 3, 480–536.

Oerter, K.E., Munson, P.J., McBride, W.O., Rodbard, D. (1990). Computerized estimation of size of nucleic acid fragments using the four-parameter logistic model. Anal. Biochem. 189, 235–243.

Remmers, E.F., Goldmuntz, E.A., Cash, J.M., Crofford, L.J., Misiewicz-Poltorak, B., Zha, H., Wilder, R.L. (1992). Genetic map of 9 polymorphic loci comprising a single linkage group on rat chromosome 10: evidence for linkage conservation with human chromosome 17 and mouse chromosome 11. Genomics 14, 618–623.

Remmers, E.F., Goldmuntz, E.A., Cash, J.M., Zha, H., Crofford, L.J., Misiewicz-Poltorak, B., Mathern, P., Wilder, R.L. (1993). Map of seven polymorphic markers on rat chromosome 14: linkage conservation with human chromosome 4. Mammalian Genome 4, 90–94.

Sano, H., Forough, R., Maier, J.A.M., Case, J.P., Jackson, A., Engleka, K., Maciag, T., Wilder, R.L. (1990). Detection of high levels of heparin binding growth factor-1 (acidic fibroblast growth factor) in inflammatory arthritic joints. J. Cell Biol. 110, 1417–1426.

Serikawa, T., Kuramoto, T., Hilbert, P., Mori, M., Yamada, J., Dubay, C.J., Lindpaintner, K., Ganten, D., Guénet, J.-L., Lathrop, G.M., Beckmann, J.S. (1992). Rat gene mapping using PCR-analyzed microsatellites. Genetics 131, 701–721.

Szpirer, C., Riviere, M., Szpirer, J., Genet, M., Dreze, P., Islam, M.Q., Levan, G. (1990). Assignment of 12 loci to rat chromosome 5: evidence that this chromosome is homologous to mouse chromosome 4 and to human chromosomes 9 and 1 (1p arm). Genomics 6, 679–684.

Truett, G.E., Bahary, N., Friedman, J.M., Leibel, R.L. (1991). Rat obesity gene fatty (*fa*) maps to chromosome 5: evidence for homology with the mouse gene diabetes (*db*). Proc. Natl. Acad. Sci. USA 88, 7806–7809.

Wilder, R.L., Calandra, G.B., Garvin, J., Wright, K.D., Hansen, C.T. (1982). Strain and sex variation in the susceptibility to streptococcal cell wall-induced polyarthritis in the rat. Arthritis Rheum 25, 1064–1072.

Zha, H., Wilder, R.L., Goldmuntz, E.A., Cash, J.M., Crofford, L.J., Mathern, P., Remmers, E.F. (1993). Linkage map of 10 polymorphic markers on rat chromosome 2. Cytogenet. Cell Genet. 63, 117–122.