Proc. Natl. Acad. Sci. USA
Vol. 90, pp. 9499–9503, October 1993
Genetics

Genetic mapping of tumor susceptibility genes involved in mouse plasmacytomagenesis

BEVERLY A. MOCK*, MARIANNE M. KRALL, AND JENNIFER K. DOSIK

Laboratory of Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892

Communicated by Michael Potter, July 15, 1993

ABSTRACT **Plasmacytomas (PCTs) were induced in 47% of BALB/cAnPt mice by the intraperitoneal injection of pristane, in 2% of (BALB/c × DBA/2N)F_1, and in 11% of 773 BALB/cAnPt × (BALB/cAnPt × DBA/2N)F_1 N2 backcross mice. This result indicates a multigenic mode of inheritance for PCT susceptibility. To locate genes controlling this complex genetic trait, tumor susceptibility in backcross progeny generated from BALB/c and DBA/2N (resistant) mice was correlated with alleles of 83 marker loci. The genotypes of the PCT-susceptible progeny displayed an excess homozygosity for BALB/c alleles within a 32-centimorgan stretch of mouse chromosome 4 (>95% probability of linkage) with minimal recombination (12%) near *Gtl0*. Another susceptibility gene on mouse chromosome 1 may be linked to *Fcgr2* (90% probability of linkage); there were excess heterozygotes for *Fcgr2* among the susceptible progeny and excess homozygotes among the resistant progeny. Regions of mouse chromosomes 4 and 1 that are correlated with PCT susceptibility share extensive linkage homology with regions of human chromosome 1 that have been associated with cytogenetic abnormalities in multiple myeloma and lymphoid, breast, and endocrine tumors.**

Plasmacytomas (PCTs) are tumors of mature end-stage B cells that can be induced in high frequency in genetically susceptible strains of mice such as BALB/cAn and NZB/BINJ by the i.p. administration of plastics, paraffin oils, or pristane (1–5). Most other inbred strains of mice are resistant to PCT induction by these agents. The incidence of induced PCTs in backcross and recombinant inbred mice derived from resistant (R) and susceptible (S) progenitors has indicated that PCT susceptibility is under multigenic control (6–10).

To localize genes involved in plasmacytomagenesis, associations of tumor susceptibility with alleles of genetic markers distributed across the mouse genome were examined in backcross progeny from a cross of S (BALB/c) and R (DBA/2) strains of mice. Our approach was similar to that used in the dissection of complex genetic traits associated with other disease processes (11–14). The genotypes of the mice that developed PCTs were examined for homozygosity (C/C) at specific loci or sequence tagged sites (STSs). In this study, regions of mouse chromosome (Chr) 4 and Chr 1 have been implicated in the genetic control of plasmacytomagenesis.

MATERIALS AND METHODS

Tumor Induction. A panel of 821 backcross progeny was generated from a cross between 24 BALB/cAnPt (PCT-susceptible) females and 8 (BALB/cAnPt × DBA/2N)F_1 (PCT-resistant) males; these mice were bred and maintained in our closed conventional mouse colony. Six- to 10-week-old mice [100 BALB/cAnPt, 100 (C × D)F_1, and 773 first generation backcross progeny] were inoculated i.p. with three 0.5-ml injections of pristane (2,6,10,14-tetramethylpentadecane) on days 0, 60, and 120.

Diagnosis. Starting at day 134, Giemsa-stained slides of ascites smears from peritoneal exudate cells were examined on a biweekly basis for the presence of atypical plasma cells. Mice were diagnosed as PCT-positive when accumulations of 10 or more atypical plasma cells were seen in the ascites smears. At this time, ascites samples from individual tumor-bearing mice were transferred i.p. to pristane-pretreated CDF_1 hybrids for purposes of generating tumor tissue for viable freezing and immortalization. Host (spleen, kidney, and liver) and tumor (mesenteric oil granuloma) tissues were removed and frozen in liquid nitrogen.

Marker Typing and Molecular Analyses of Tumors. DNA isolation (tumor and kidney), restriction enzyme digestion, agarose gel electrophoresis, Southern blotting, and restriction fragment length polymorphism (RFLP) analyses were performed as described (15). D4Rck clones were amplified and labeled by PCR as described (16). Simple sequence length polymorphism (SSLP) analyses of the simple sequence repeats (SSRs) were a modification of those previously described (17). Several probes and RFLPs for loci and SSRs examined for associations with tumor susceptibility are described in Table 1. In addition to the markers described in Table 1, the following loci or SSRs were examined for associations with tumor susceptibility: (Chr 2: *Neb, D2Mit21*; Chr 3: *D3Mit21, Egf*; Chr 5: *D5Mit1, Nmyc-2, Gus*; Chr 6: *Met, D6Mit8, D6Mit14*; Chr 7: *Ccnb1-rs9, Mtv-1, D7Mit46, D7Mit15*; Chr 8: *D8Mit16, D8Mit14*; Chr 9: *D9Mit22, Cck*; Chr 10: *Myb, Gli*; Chr 11: *D11Mit2, Sparc, Cchlb1, Nm23, Gfap, Pkca*; Chr 12: *D12Mit4, D12Lgm1*; Chr 13: *D13Mit3, Il-9*; Chr 14; *Rb-1, D14Mit35*; Chr 15: *Rpl30, Ly-6, Gdc-1*; Chr 16: *Prm-1, D16Mit4*; Chr 17: *D17Mit30, Nec 1.7, Qa-2,3, D17Mit3, D17Mit41*; Chr 18: *D18Mit22, Ii, D18Mit7*).

Probes used to detect rearrangements in tumor DNAs cut with *Bam*HI and *Eco*RI were the 6.5-kb *Bam*HI–*Eco*RI fragment of pECκ and the 1.7-kb *Hin*dIII–*Xba* I fragment of pIVS, which detect the joining (J), constant (C), and intervening sequence regions of the *Igk* locus (18), the 700-bp *Pst* I fragment of pλ2 (19), which detects the C region of *Igl*, the 1.0-kb *Bam*HI fragment of pJ_0 and the 2.0-kb *Eco*RI–*Bam*HI fragment of pJ_{11}, which detect the *Igh* J regions 1–4 (20), and the 1.7-kb *Hin*dIII fragment of pMmyc54 (21) and the 5.5-kb *Bam*HI fragment of S107, which detect exons 1–3 of the *Myc* oncogene (22). Additional rearrangements were detected with pMmyc54 upon hybridization to *Eco*RV-digested DNAs. Immunoglobulin κ and λ light chain gene rearrangements were detected in 83% and 12% of the primary tumor DNAs examined, respectively. In addition, 88% of the primary tumors had immunoglobulin heavy chain rearrange-

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Abbreviations: PCT, plasmacytoma; Chr, chromosome; R, resistant; S, susceptible; STS, sequence tagged site; RFLP, restriction fragment length polymorphism; SSLP, simple sequence length polymorphism; SSR, simple sequence repeat; lod, $\log_{10}$ of the odds; DLLC, diffuse lymphoma with a large cell component.

*To whom reprint requests should be addressed at: Building 37, Room 2B-08, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.

ments. Seventy-eight percent of the PCTs had detectable *Myc* rearrangements and roughly 65% of them had both *Igh* and *Myc* rearrangements.

Statistical Analyses. The associations of tumor susceptibility with alleles of the markers were evaluated by a χ^2 test of frequencies of heterozygous (C/D) and homozygous (C/C) PCT-positive mice, similar to methods described previously (13, 23). When χ^2 values exceeded 3, additional S and R backcross progeny were examined to check for effects of segregation distortion. These classes were evaluated by a χ^2 test of independence [1 degree of freedom (df)] using the formula $\chi^2 = (ad - bc)^2 n/(a + b)(c + d)(a + c)(b + d)$ as outlined in Sokal and Rohlf (24); a and b are the number of susceptible (PCT^+) heterozygotes and homozygotes, respectively, and c and d are the number of resistant (PCT^-) heterozygotes and homozygotes, respectively. Associations were considered significant when χ^2 values exceeded 11.7 [a value equivalent to a 95% probability of linkage in mouse backcrosses (P. Neumann, personal communication)] or 13.8 [a value equivalent to a $\log_{10}$ of the odds (lod) score of 3 (25)]. The relationship between χ^2 values and posterior probabilities of linkage in mouse backcrosses were evaluated in Bayesian analysis in a manner similar to the analysis of recombinant inbred strains (26). lod scores were obtained with the aid of E. Remmers using MAPMAKER (V 1.9, obtained from E. Lander at MIT, Cambridge, MA) on a VAX minicomputer. Maximum likelihood estimates of recombination probabilities [c = recombinants (r)/total number (n)] and standard errors among backcross progeny were calculated according to Green (27). Gene order was determined by minimizing the number of recombination events among the allele distribution patterns of markers across the chromosome and performing 3-point linkage analyses (linkage criteria: lod = 3, $\theta = 0.35$) using MAPMAKER (V 1.9).

RESULTS

Tumor Incidence Patterns in Backcross Progeny. To identify locations of genes contributing to the inheritance of susceptibility to plasmacytomagenesis, the incidence of pristane-induced tumors was evaluated in 773 backcross progeny from the cross BALB/cAnPt × (C × D)F_1. BALB/cAnPt mice were susceptible (47% of the mice developed tumors) to plasmacytomagenesis by 400 days after pristane injection, whereas (C × D)F_1 hybrids were resistant (98% tumor-free) (Fig. 1). Only 11% (83/773) of the backcross progeny developed tumors by 400 days after pristane. This incidence was the same as that observed previously (9) and represents a significant deviation away from the 23.5% expected for a single gene trait ($\chi^2 = 6.65$, $P = 0.01$), indicating that inheritance of PCT susceptibility is likely to be under multigenic control. Six of the 83 tumor-bearing backcross progeny died (without autopsy), leaving a total of 77 susceptible backcross progeny available for marker analyses. In addition, 68 resistant backcross progeny were subjected to marker analyses. It should be noted that progeny designated as "resistant" may include some genetically susceptible individuals, since only 47% of the susceptible parent (BALB/c) develop tumors.

Associations of DNA Markers with Plasmacytomagenesis. RFLPs and SSLPs between the DNAs of BALB/c and DBA/2 mice for a panel of 83 markers distributed across the mouse genome were used to examine the cosegregation of tumor susceptibility with alleles/variants of the marker loci. A minimum of two markers (one proximal and one distal) per chromosome was chosen for evaluation, excepting the markers evaluated for distal Chr 16 where no polymorphisms between BALB/c and DBA/2 were detected. Associations of susceptibility with BALB/c alleles of marker loci were analyzed by χ^2. As an initial screen, the first 28 mice to develop tumors were evaluated for their genotypes with a genome-wide panel of markers. χ^2 values for the majority of markers examined ranged from 0.04 to 2.46. Significant associations between tumor susceptibility and the presence of homozygosity of BALB/c alleles were observed for markers on mouse Chr 4 (Table 1). χ^2 values exceeding the 11.7–13.8 range were obtained for the markers *Ifa, Mtv-13*, and *Pnd* located in the distal portion of Chr 4 (Table 1).

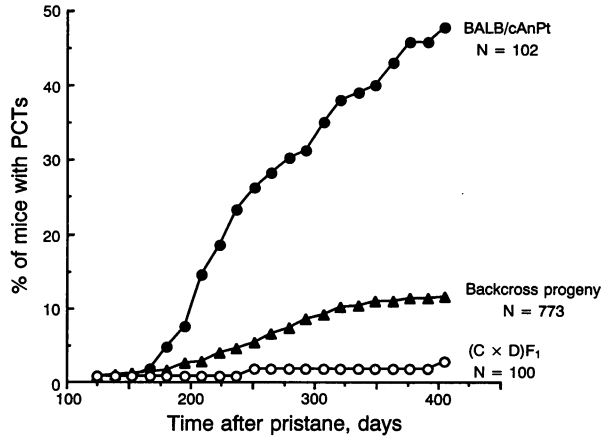

FIG. 1. Incidence of PCTs in BALB/cAnPt, (C × D)F_1, and 773 backcross progeny generated from a cross between BALB/cAnPt females (PCT-susceptible) and (BALB/cAnPt × DBA/2NPt)F_1 males (PCT-resistant).

In contrast to the Chr 4 markers where the susceptible backcross progeny were homozygous (C/C), there were two chromosomal regions in which excess numbers of heterozygous (C/D) individuals were observed among the susceptible progeny. χ^2 values of 10.3 and 5 were obtained for the markers *Fcgr2* on Chr 1 (90% probability of linkage) and *Ly-1* on Chr 19 (<50% probability of linkage) (Table 1). The markers examined on Chr 1 also revealed an excess of homozygotes among the resistant backcross progeny, suggesting an allelic association. Although these χ^2 values were lower than the 11.7–13.8 range considered to be significant evidence of linkage, they are higher than expected and present the possibility of additional modifying genes involved in PCT formation.

PCT Susceptibility (*Pcts*) Is Linked to Distal Chr 4 Near *Gt10*. Given our initial results with positive associations between tumor susceptibility and the three Chr 4 markers, *Ifa, Mtv-13*, and *Pnd*, we intensified our efforts on distal Chr 4 to produce a high-resolution map across the region of PCT susceptibility. Haplotype (data not shown), χ^2 (Table 1), and lod score (Fig. 2*A*) analyses of the 77 susceptible and 68 resistant backcross progeny for 22 markers spanning the length of Chr 4 revealed that the most closely linked marker to tumor susceptibility was *Gt10* (gene trap insertion site 10). Its association with PCT susceptibility yielded a χ^2 value of 28.7 with 9 recombinants (heterozygotes) out of the 77 susceptible progeny for a lod score equivalent to 11.12. Thus, the most probable location for *Pcts* gene(s) is within 11.6 ± 3.6 cM of *Gt10*.

Another Susceptibility Gene May Be Linked to Distal Chr 1 Near *Fcgr2*. χ^2 (Table 1) and lod score (Fig. 2*B*) analyses of roughly 77 susceptible and 68 resistant backcross progeny for 10 markers spanning Chr 1 revealed potential linkage of another *Pcts* gene to the marker *Fcgr2* (low-affinity Fc IgG receptor 2). Evaluation of additional markers is needed to confirm or reject linkage of tumor susceptibility/resistance to this chromosome.

DISCUSSION

A major genomic region influencing susceptibility to PCT development has been mapped in crosses of S (BALB/cAn) and R (DBA/2) strains of inbred mice. This region has been localized to the distal portion of mouse Chr 4 near *Gt10* (in a

Table 1. Association of PCT susceptibility with RFLP/SSLP markers

Chr	cM	Probe	Enzyme	C	D	r/*n*	c	PCT$^+$/ Het	PCT$^+$/ Hom	PCT$^-$/ Het	PCT$^-$/ Hom	χ^2	*P*	Ref(s).
1	24	*Tnp-1*	*Hin*dIII	9.4	9.2	44/76	0.58	44	32	35	33	0.6	<0.1	28
	25	*Il8rb*	*Msp* I	5	4.2	41/73	0.56	41	32	35	33	0.32	<0.5	29
	25	*Vil*	*Xba* I	6.8	20	42/75	0.56	42	33	34	34	0.52	<0.1	30
	28	*Acrg*	*Xba* I	1.8	2.3	45/77	0.58	45	32	31	37	2.39	<0.1	31
	33	*Bcl-2*	*Xba* I	5	5.8	46/77	0.6	46	31	29	39	4.23	<0.05	31
	37	*Ren1*	*Eco*RI	—	4.3	48/77	0.62	48	29	28	40	6.48	<0.025	32
	48	*D1Mit16*	SSLP	0.19	0.201	47/74	0.64	47	27	25	41	9.93	<0.005	17
	54	*Fcgr2*	*Bam*HI	9.8	9.2	50/77	0.65	50	27	26	42	10.32	<0.005	33
	60	*Mtv-7*	*Eco*RI	—	11.7	49/77	0.64	49	28	27	39	7.37	<0.01	34
	63	*Adprp*	*Hin*dIII	22.0, 4.4	23.0, 4.3	46/75	0.61	46	29	28	39	5.42	0.025–0.01	35
4	10	*Mtv-14*	*Eco*RI	—	1.7	35/77	0.45	35	42	34	34	0.3	<0.5	36, 37
	14	*D4Lgm2*	*Pvu* II	4.2	3.3, 1.0	37/77	0.48	37	40	34	34	0.06	0.9	37
	31	*D4Lgm4*	*Msp* I	4.7	10.2	29/77	0.38	29	48	38	30	4.82	<0.05	37
	43	*D4Rck83*	*Bam*HI	20	2	23/77	0.3	23	54	38	30	10.03	<0.005	16
	50	*Ifa*	*Pvu* II	5.8	5.7	15/77	0.19	15	62	36	32	17.73	<0.001	38
	54	*D4Rck12*	*Xba* I	2.2	3	13/77	0.17	13	64	35	33	19.51	<0.001	16
	56	*Scl*	*Pvu* II	4.4	4	12/77	0.16	12	65	35	33	21.23	<0.001	39
	56	*D4Lgm1*	*Bgl* II	14.2	9.4	13/77	0.17	13	64	35	33	19.51	<0.001	37
	56	*D4Rp1*	*Eco*RI	4.1	3.7	13/77	0.17	13	64	35	33	19.51	<0.001	40
	56	*Mtv-13*	*Eco*RI	—	9.4	12/77	0.16	12	65	35	33	21.23	<0.001	34
	57	*D4Mit37*	SSLP	0.232	0.22	13/77	0.17	13	64	33	35	16.7	<0.001	17
	58	*D4Rck41*	*Eco*RV	9.7	26	13/77	0.17	13	64	34	34	18.08	<0.001	15
	58	*Ccnb1-rs10*	*Eco*RI	9.3	9.2	13/77	0.17	13	64	34	34	18.08	<0.001	41
	69	*Gt10*	*Xba* I	12	20	9/77	0.12	9	68	36	32	28.71	<0.001	42
	69	*D4Mit32*	SSLP	0.184	0.142	10/77	0.13	10	67	36	32	26.61	<0.001	17
	71	*D4Mit13*	SSLP	0.092	0.097	12/77	0.16	12	65	37	31	24.33	<0.001	17
	75	*D4Lgm3*	*Stu* I	6.6	6.2, 4.4	11/77	0.14	11	66	35	33	23.05	<0.001	37
	75	*Tnfr-1*	*Bam*HI	6.6	10	10/77	0.13	10	67	36	32	26.61	<0.001	43
	76	*Pnd*	*Acc* I	6.8	7.9	11/77	0.14	11	66	36	32	24.63	<0.001	44
	80	*D4Mit33*	SSLP	0.128	0.144	14/77	0.18	14	63	38	30	22.31	<0.001	17
	81	*D4Mit42*	SSLP	0.102	0.091	15/77	0.19	15	62	38	30	20.63	<0.001	17
	83	*D4Smh6b*	*Sph* I	9.6	12	17/77	0.22	17	60	38	30	17.53	<0.001	45
19	5	*Ly-1*	*Eco*RI	19	8.8	53/75	0.71	53	22	46	40	4.99	<0.05	46, 47
	10	*D19Mit16*	SSLP	0.136	0.118	49/71	0.69	49	22	14	12	3.11	<0.1	17
	23	*D19Mit13*	SSLP	0.246	0.262	46/72	0.64	46	26	13	13	1.54	<0.5	17
	25	*Fas*	*Stu* I	9.5	8	45/77	0.58	45	32	46	41	0.51	<0.5	

The chromosomal location [in centimorgans (cM) from the centromere] of the markers, the restriction endonuclease used to detect RFLPs, and the fragment sizes (in kb) detected between BALB/c (C) and DBA/2N (D) are indicated on the left. The recombination fraction (c) represents the number of tumor-positive heterozygotes (r) over the total number (*n*) of susceptible progeny examined by RFLP/SSLP analysis. The number of PCT-susceptible (PCT$^+$) and PCT-resistant (PCT$^-$) heterozygotes (Het) and homozygotes (Hom) are indicated in columns on the right. χ^2 values (1 df) and associated critical values (*P*) for detecting significant associations of markers with the susceptibility phenotype are also indicated. The references indicated are for probes or markers used in the RFLP/SSLP analyses and consensus map locations. Map distances and gene order for markers were determined by minimizing the number of recombinants among the backcross progeny.

region syntenic with human Chr 1) by analyzing a series of 83 allelomorphic markers distributed throughout the genome. The haplotype and lod score analyses for 22 of these markers suggest that a probable location for *Pcts* is within 11 cM of the marker, *Gt10*.

The apparent recombination frequencies between *Pcts* and either *D4Rck41*/*Ccnb1-rs10* (0.16) or *Gt10* (0.12) (Table 1) were greater than expected if *Pcts* is located within the 11-cM interval between these markers (Fig. 2*A*). This could result from the segregation of other tumor susceptibility or modifying genes, or possibly somatic mutations in unlinked genes (creating the potential for sporadic, nonheritable tumors), both of which could create the difference between the true and apparent recombination frequencies in PCT-susceptible mice.

Another genomic region influencing the development of tumors in the backcross progeny may be linked (90% probability) to *Fcgr2* in the distal portion of mouse Chr 1 (also sharing linkage homology with human Chr 1). In contrast to the linkage of *Pcts* to Chr 4, where 88% of the susceptible backcross progeny were homozygous (C/C) for the *Gt10* marker, linkage to Chr 1 was detected as greater numbers of heterozygotes (C/D) among the susceptible progeny and homozygotes (C/C) among the resistant progeny than expected. If not spurious, the results with *Fcgr2* suggest that the DBA/2 allele of a linked *Pcts* gene is associated with susceptibility and that the BALB/c allele is associated with resistance. This could account for the "leaky" phenotype of the F_1 hybrid in which 2% of the (C × D)F_1 mice developed tumors. Tumors may also arise as a result of changes in gene dosage; cells carrying only one copy of an implicated gene may make less of a gene product required for normal growth or differentiation (49, 50).

In a separate effort to identify and characterize the biological action of PCT resistance genes in DBA/2 mice, Potter and colleagues (51) have created a series of C.D2 bilineal congenic strains in which DBA/2 genes from selected regions across the genome have been introgressively backcrossed onto the BALB/c background. They have identified two regions in the distal portion of mouse Chr 4 that contribute to the resistance phenotype of DBA/2N mice (M. Potter, personal communication). The small number (n = 77) of susceptible backcross progeny examined in the current series of mice does not allow for the confirmation or rejection of two closely linked *Pcts* genes on Chr 4.

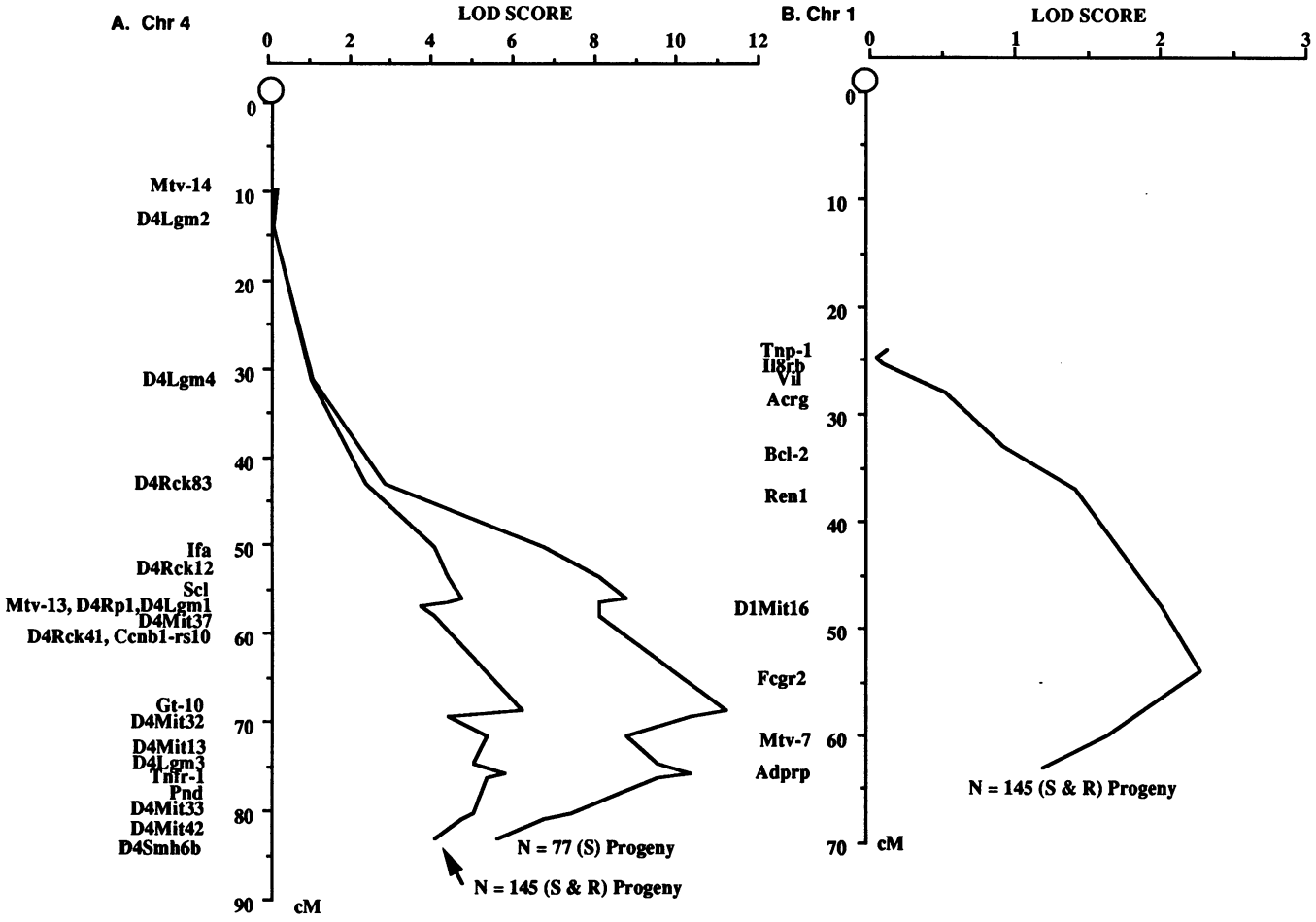

FIG. 2. Likelihood map of lod scores for PCT susceptibility with genetic markers spanning the length of mouse Chr 4 (*A*) or Chr 1 (*B*). The RFLP linkage map of the chromosome is indicated on the vertical axis. The maximum likelihood positions for *Pcts* genes are near the highest point on the curves that peak at *Gt10* (*A*) and *Fcgr2* (*B*). Genetic maps of Chr 4 and Chr 1 are based on the haplotype data from progeny of the intraspecific cross BALB/cAnPt × (BALB/cAnPt × DBA/2NPt)F_1. The loci or STSs mapped in the cross are indicated on the left. Recombination distances in cM from the centromere are shown to the left of the chromosome. *Mtv-14* was positioned at 9.8 cM (*A*) and *Tnp-1* was positioned at 24 cM (*B*) from the centromere based on consensus map data (36, 48).

Cytogenetic abnormalities of human Chr 1 have been detected in a variety of neoplasms (52, 53). Translocations, deletions, and duplications involving different sections of Chr 1 are frequently found in acute leukemias (54) and a variety of solid tumors (55). Loss of heterozygosity (LOH) studies involving human 1p and 1q for a variety of cancers (53) have led to the proposition that a tumor suppressor gene may reside on human Chr 1. A suppressor role for both mouse Chr 4 and human Chr 1 has emerged from hybrid cell fusion studies of normal and malignant cells (56–58). These studies provide a basis for an analysis of our (C × D)F_1 tumor cell lines for LOH events.

Of relevance to mouse PCTs are the cytogenetic studies involving patients with multiple myeloma, Burkitt lymphoma, plasma cell leukemia, and non-Hodgkin lymphoma of the DLLC (diffuse lymphoma with a large cell component) type. Although these various tumors exhibit distinct phenotypes, they do have biological and cytogenetic features in common with mouse PCTs. Cytogenetic studies in multiple myeloma patients (prior to treatment) have revealed that the most commonly affected chromosomes have been Chr 1 and Chr 14 (59). Common abnormalities include chromosomal breakpoints (59–63) and deletions or duplications (59, 64, 65) of the chromosome ranging from 1p11-35 and 1q22-43. In addition, tumor samples from 10 Burkitt lymphoma patients had partial trisomy for Chr 1q (62), bone marrow cells from a single patient with a plasma cell leukemia were carrying a translocation involving Chr 1 and Chr 6 (66), and 28 DLLC samples had chromosomal breaks at either 1p32-36 or 1p22 (67). In fact, patients with DLLC and breaks at 1q21-23 or 1p32-36 were associated with both a shortened median survival and a decreased probability of achieving remission (67).

The localization of *Pcts* to the distal region of mouse Chr 4 is a first step in identifying candidate loci for susceptibility genes involved in pristane-induced plasmacytomagenesis. This region of mouse Chr 4 shares a high degree of linkage homology with human Chr 1. More than 20 loci residing in the 32-cM region spanning the distal half of Chr 4 from *Jun* to *Ski* have been mapped to human Chr 1p32-36 and 1q22-24 (36). In addition, genes in the distal portion of mouse Chr 1 also share linkage homology with human Chr 1q21-41 (48). Thus, the identification of chromosomal locations for *Pcts* genes gives a new direction for genetic studies of mouse plasmacytomagenesis that may also be extended to familial and case-control studies of multiple myeloma, which have traditionally concentrated on examining genetic associations with HLA antigens (68). *Gt10* and surrounding loci now provide good markers to use as start points in the fine mapping of *Pcts* and to search for associations with human PCTs, multiple myeloma, and DLLC.

We thank Eric Lander, Paul Neumann, John Todd, and Michael Cole for advice and suggestions during the formulation of these studies. We appreciate the excellent technical assistance of Glenn

Arzadon, Monica Bright, Danielle Holiday, and Archana Aggarwal. In addition, we wish to thank Ed Kuff, Kira Leuders, Paul Neumann, Nancy Jenkins, Neal Copeland, Richard Nordan, and two anonymous reviewers for critical readings of earlier versions of the manuscript. The following investigators kindly provided probes and/or primer sequences that made the marker analyses possible: G. Bell, B. Blackwood, R. Bernards, A. Bothwell, S. Brown, R. Callahan, D. P. Cerretti, H. Chin, N. Copeland, N. J. Cowan, W. Dietrich, R. Eisenmann, R. Elliott, J. Friedman, R. Ganschow, D. Givol, R. Goodwin, J.-L. Guenet, P. Hamel, J. Hanley-Hyde, P. Hausner, N. Hecht, M. Heller, L. Herzenberg, B. Hogan, K. Huppi, N. Jenkins, A. Joyner, I. Kirsch, L. Kozak, E. Lander, F. McCormick, J. P. Merlie, J. Mullins, J. F. Mushinski, R. Perry, P. Pitha, J. Ravetch, R. Reeves, J. E. Richards, S. Rudikoff, E. Schon, P. Steeg, G. Van de Woude, J. Van Snick, L. Stubbs, and B. Vogelstein. Our mice were housed at Organon Teknika (Rockville, MD) under National Cancer Institute Contract NO1-CB-21075.

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