

GENE MAPPING OF THE THREE SUBUNITS OF THE HIGH AFFINITY FcR FOR IgE TO MOUSE CHROMOSOMES 1 AND 19

KONRAD HUPP,¹* DAVID SIWARSKI,* BEVERLY A. MOCK,* AND JEAN-PIERRE KINET[†]

From the *Laboratory of Genetics, National Cancer Institute, and the †Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal Skin Diseases, National Institutes of Health, Bethesda, MD 20892

The high affinity receptor for IgE (FcεRI) is a tetrameric structure consisting of a single IgE-binding α subunit, a single β subunit, and two disulfide-linked γ subunits. The α subunit of FcεRI and most Fc receptors are homologous members of the Ig superfamily. By contrast, the β and γ subunits from FcεRI are not homologous to the Ig superfamily. The γ chains do share a region of high homology with the ζ-chain of the TCR. No homology has been found to date for β with any published sequence. Here, we report that a single copy gene encodes FcεRIβ and that the locus for FcεRIβ is found on mouse chromosome 19, genetically linked to the Ly-1 (Ly-12) locus and in a region that also contains Ly-10 and Ly-44 (CD20). Homology comparisons among these molecules reveal limited regions of homology between FcεRIβ and Ly-44 (CD20) as well as other striking similarities: both molecules have four putative transmembrane segments and a probable topology where both amino- and carboxytermini protrude into the cytoplasm. In addition, we show that a single gene for FcεRIγ is found at the distal end of mouse chromosome 1, clustered in a region where FcεRIα has also been linked to FcγRII. At least one of the two forms of FcγRII has recently been shown to contain γ subunits identical to the γ subunits of FcεRI. The close association of the genes for FcεRIα, FcγRII, and their shared γ subunits raises interesting implications regarding coordinate regulation of gene expression.

FcεRI² is found exclusively on mast cells and basophils. When challenged with multivalent Ag, the receptor-bound IgE triggers cell degranulation and the release of mediators responsible for allergic symptoms (1). FcεRI is a tetrameric complex (αβγ₂) consisting of noncovalently associated subunits (2). We and others have reported the cloning of complementary DNA (cDNA) for the rat (3) and human α subunit (4, 5) and the genomic structure of the rat α gene has now been reported (6). We have also isolated cDNA for the rat β (7) and γ (8) and more recently

for the mouse α, β, and γ.³ Efficient expression of FcεRI on the surface of transfected cells required cotransfection of the three subunits, suggesting that αβγ₂ is the minimal structure for FcεRI (8). Sequence analysis of all three subunits shows that the IgE-binding α subunit—but not the β and γ subunits of FcεRI belong to the Ig superfamily.

Most FcR show considerable homology with members of the Ig superfamily but unlike FcεRI, have been thought to consist of single Ig-binding subunits. However, we recently demonstrated that at least one Fcγ receptor (FcγRIIa) is also associated with a subunit identical to γ from FcεRI⁴.

Gene mapping from this laboratory and others (9–12) have demonstrated that many FcR genes (including FcεRIα) are clustered at the distal end of mouse chromosome 1. In addition to implicating a common evolutionary origin, we have speculated that this cluster of genes is important in coordinate regulation of tissue-specific expression of FcR (12). We now demonstrate that the γ-chain of FcεRI is encoded in a single gene that maps close to FcγRII. This finding may have a functional relevance because at the protein level, both FcεRIα and FcγRII associate with γ-chains. We also show that the β-chain of FcεRI is encoded by a single gene and is linked to Ly-1 on mouse chromosome 19 in a region that contains other lymphocyte differentiation Ag such as Ly-44 (CD20). Because of the colocalization of these genes, we have searched for and identified limited sequence homologies and similarities between Ly-44 and FcεRIβ.

MATERIALS AND METHODS

Mice. Inbred, congenic or recombinant inbred (RI) strains of mice were obtained from the following sources: C57BL/6J, C57L/J, C58/J, SWR/J, BXD RI strains, and AKXL RI strains (The Jackson Laboratory, Bar Harbor, ME); AKR/N, BALB/cAn, C57BL/10N, DBA/2N, NZB/B1NJ, SJL/JLW, BALB/cAn.DBA/2N (C.D2) Ly-1^c/Ly-1^d, C.D2 Pep-3^b/Akp-1^b, and (BALB/cAn × DBA/2N) F₁ × DBA/2N (Hazleton Laboratories, Rockville, MD); CXS RI strains and 020/A (The Netherlands Cancer Institute, Amsterdam, The Netherlands).

Hybridization probes. The cDNA probe for mouse FcεRIα is a 600-bp StyI restriction fragment described previously (3). FcεRIβ is a 910-bp insert containing the full length cDNA derived from mouse.² The FcεRIγ probe is a 200-bp BamHI-EcoRI insert derived as a cDNA clone from rat RBL (8). The TCR Zeta probe is a 0.9-kb BamHI-XbaI cDNA insert generously supplied by Dr. R. Klausner, National Institutes of Health, Bethesda, MD (13).

Preparation of DNA and Southern hybridizations. DNA was extracted from frozen liver or splenic tissue as previously described (14). The restriction digestion, electrophoresis, and Southern hybrid-

³ Ra, C., M.-H. E. Jouvin, and J.-P. Kinet. Complete structure of the mouse mast cell receptor for IgE (FcεRI) and surface expression of chimeric receptors (rat-mouse-human) on transfected cells. 1989. *J. Biol. Chem.* 264:15323.

⁴ Ra, C., M.-H. E. Jouvin, U. Blank, and J.-P. Kinet. *Nature*. In press.

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¹ Address correspondence and reprint requests to Dr. Konrad Huppi, Laboratory of Genetics, NCI, NIH, Bldg. 37, Rm. 2B-21, Bethesda, MD 20892.

² Abbreviations used in this paper: FcεRI, high affinity receptor for IgE; FcR, Fc receptor; SDP, strain distribution pattern; RI, recombinant inbred; BXD, C57BL/6J × DBA/2J; AKXL, AKR/J × C57L/J; CXS, BALB/cHeA × STS/A; OXA, 020/A × AKR/FuRdA.

ization conditions have also been described. Briefly, DNA was restricted with the appropriate restriction endonuclease, electrophoresed in 0.7% agarose gels, and transferred to Nylon filters. The final wash stringency for all hybridizations shown was $0.2 \times \text{SSC}$ ($1 \times \text{SSC} = 0.15 \text{ M}$ sodium chloride, 0.015 M sodium citrate) at 65°C for 30 min.

Genetic crosses and recombination frequencies. The CXS recombinant inbred series consist of 14 strains inbred more than 30 generations and typed for nearly 100 polymorphic loci (15). The CXS tissue was obtained through the generosity of J. Hilgers Amsterdam, The Netherlands. The C57BL/6J $\times$ DBA/2J and AKR/J $\times$ C57L/J recombinant inbred series obtained from The Jackson Laboratory are essentially 26 and 18 strains, respectively. Genetic distances were calculated by using the method of Silver and Buckler (16). Gene order is based on minimization of recombination frequencies between loci.

RESULTS

Fc ϵ RI β and Fc ϵ RI γ are found as polymorphic single genes. Originally, we showed by Southern analysis that Fc ϵ RI α is a single gene (12). Recent cloning of the β and γ subunits has inferred that these genes may be present in single copies in the rat (7, 8) and mouse.² The intensity of the *Eco*RI RF bands shown here (Fig. 1) as well as the RF patterns observed with eight additional restriction endonucleases (data not shown) supports that β and γ are also found as single copy genes. A more extensive survey with these probes reveals RFLP for Fc ϵ RI γ (*Eco*RI) (Fig. 2) and Fc ϵ RI β (*Hind*III, Fig. 3 or *Taq*, Fig. 4), which identify haplotypes among mouse inbred strains. When compared, the α , β , and γ gene haplotypes do not cosegregate and therefore behave as distinct genetic loci (Table I).

BALB/cAnPt-Eco R1 Digestion

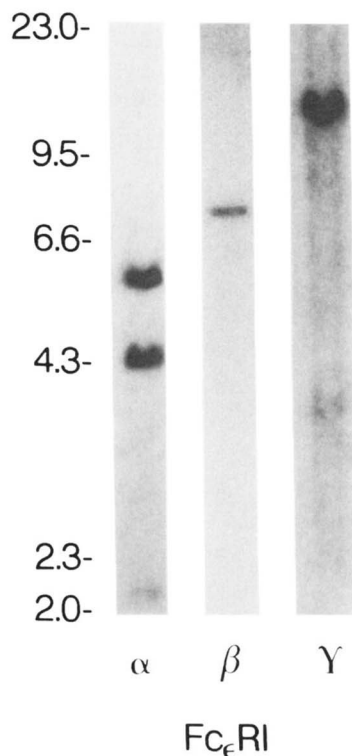
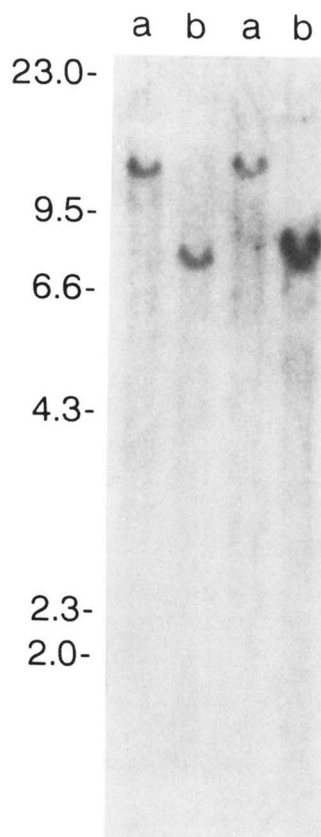


Figure 1. Southern hybridization of Fc ϵ RI cDNA probes to mouse genomic DNA. *Eco*RI digested genomic DNA from the mouse inbred strain, BALB/cAn was hybridized with the corresponding mouse cDNA probes of the three subunits of Fc ϵ RI (α , β , γ).

MOUSE INBRED STRAIN HAPLOTYPES



Fc ϵ RI γ Probe- Eco RI Digestion

Figure 2. Inbred strain haplotypes defined by an Fc ϵ RI γ *Eco*RI RFLP. Representative Fc ϵ RI γ *Eco*RI patterns are as labeled (a = NZB/BiNJ, SJL/JLw, b = 020/A, SWR/J).

Fc ϵ RI β is linked to Ly-1 on mouse chromosome 19. Our laboratory has generated congenic mice containing specific DBA/2N loci by introgressive backcrossing of BALB/c with DBA/2N. One of these congenics C.D2 Ly-1^{c/d}, selected for the Ly-1 locus of chromosome 19 was shown to contain the (DBA/2N $\times$ BALB/cAn)F1 pattern on Southern blots when tested for Fc ϵ RI β (Fig. 4). This result suggested that Fc ϵ RI β could be linked to Ly-1 on chromosome 19. The *Hind*III RFLP that we have established for Fc ϵ RI β (Fig. 3) allows us to score recombinants among several genetic crosses between β haplotypes. To confirm genetic linkage of Fc ϵ RI β and Ly-1, we compared the SDP generated by Fc ϵ RI β (*Hind*III) with previously published data for Ly-1 and Ly-10 (17). In a panel of recombinant inbred mice generated between AKR and C57L/J (AKXL), we detected significant linkage between Fc ϵ RI β , Ly-1 (15/16 concordancies), and Ly-10 (12/15 concordancies). This suggests an approximate genetic distance of 1.7 cM ($p = 0.955$) between Ly-1 and Fc ϵ RI (16).

To confirm further the linkage of Fc ϵ RI β to Ly-1, we

Inbred Strain Haplotypes

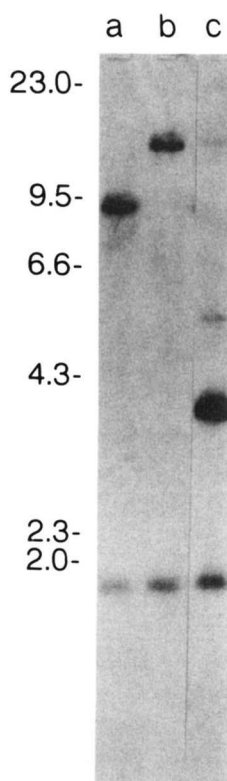
Fc ϵ RI β -Hind III Digestion

Figure 3. Inbred strain haplotypes defined by an Fc ϵ RI β HindIII RFLP. Three Fc ϵ RI β HindIII patterns are shown and are labeled accordingly (a = C58/J, b = BALB/cAn, c = SWR/J). The origin of the faint 12 kb and 5.0 kb RF bands in lane c is uncertain.

TABLE I

Comparison of α , β , and γ gene haplotypes

Inbred Strain	Inbred Strain Haplotypes		
	Fc ϵ RI α ^a	Fc ϵ RI β ^b	Fc ϵ RI γ ^c
AKR/N	a	a	a
BALB/c	a	b	b
C57BL/6J	b	a	a
C57BL/10N	b	a	a
C57L/J	b	b	a
C58/J	c	a	a
DBA/2N	b	a	b
NZB/BiNJ	a	a	b
020/A	b	a	a
SJL/JLw	a	a	b
STS/A	c	a	b
SWR/J	c	c	a

^a BamHI digestion.^b Hind III digestion.^c EcoRI digestion.

analyzed a series of (BALB/c $\times$ DBA/2) F1 $\times$ DBA/2N backcross mice for recombinants between Ly-1 and Fc ϵ RI (Table II). There were no recombinants found among 47 backcross mice, indicating Ly-1 and Fc ϵ RI β are genetically linked and may lie as close as 0.4 cM. Incidentally, Fc ϵ RI β is the first marker of chromosome 19 to be established in the recombinant inbred panel of BALB/cHeA $\times$ STS/A (Tables III, IV, and V).

Fc ϵ RI β and Ly-44 share common properties. The genetic linkage of Ly-1 and Fc ϵ RI β in a region that also contains Ly-44 (CD20) (18) encouraged us to look for

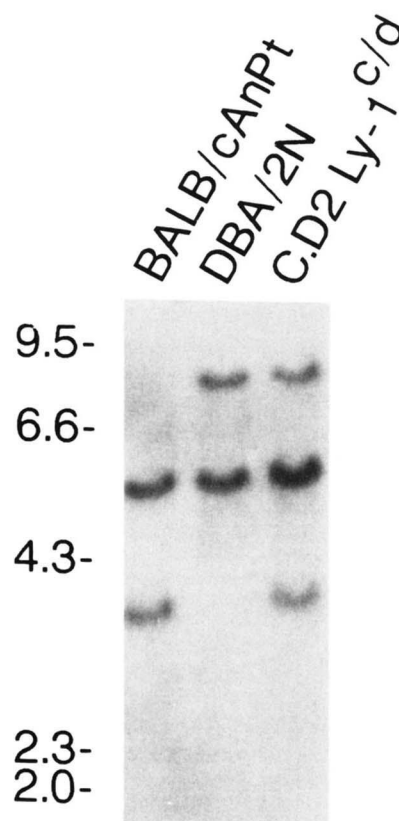
Fc ϵ RI β -Taql Digestion

Figure 4. Segregation of Fc ϵ RI β with the C.D2Ly-1 congenic. Taql digested genomic DNA from BALB/cAn, DBA/2N, and heterozygous C.D2 Ly-1^{c/d} congenic mice were hybridized to the Fc ϵ RI β cDNA probes. The persistence of a DBA/2N specific 8.0 kb Taql band in the Ly-1 congenic indicates Fc ϵ RI β has cosegregated with Ly-1.

TABLE II

Analysis of recombination frequency in (BALB/c $\times$ DBA/2N) F1 $\times$ DBA/2N backcross mice^{a,b}

Breeder	Loci		
	Ly-1	Fc ϵ RI β	N
BALB/cAn	C	C	
DBA/2N	D	D	
(BALB/c $\times$ DBA/2N)F1	C/D	C/D	
Backcross progeny F1 $\times$ DBA/2N	D/D	D/D	26
	C/D	C/D	21
	D/D	C/D	0
	C/D	D/D	0
BALB/c.DBA/2 (C.D2)Congenics	TerZ	Ly-17	Fc ϵ RI β
C.D2 Pep3/Akp-1 (chr1)	C/D	C/D	C/C
C.D2 Ly-1 (chr19)	C/C	C/C	C/D

^a C = BALB/cAn, D = DBA/2N.^b Congenic mice used in this survey are maintained as heterozygotes and therefore, contain a heterozygous RF pattern as well.

common properties between these molecules. No apparent relatedness was found between Ly-1 and Fc ϵ RI β . However, comparison between the DNA sequences of Ly-44 and Fc ϵ RI β indicated that the coding sequence of Ly-44 (bp 172–1111) is related to the 3' untranslated region of Fc ϵ RI β (bp 910–1714): 44.6% nucleotides are identical between the two sequences when an average of one gap for every 20 bp is permitted (data not shown). At the protein level, we find 29% identities between Fc ϵ RI β (residues compared are 45–141) and Ly-44 (residues com-

TABLE III
BXD strain distribution patterns

	1	2	5	8	9	11	12	13	14	15	16	19	21	22	24	25	27	28	29	30	32
Pep3	B ^a	B	D	B	B	D	B	D	B	D	B	B	B	B	D	B	D	D	D	D	D
TcrZ	B	B	D	.	D	D	B	D	B	D	B	.	B	D	D	D	.	D	D	D	D
At-3	B	B	D	B	D	D	B	D	B	B	B	B	B	D	D	D	D	D	D	D	D
ADPRP	B	B	D	B	D	D	B	B	B	B	B	B	B	D	D	D	D	D	D	D	D
Fc γ RII(Ly-17)	B	D	D	D	D	D	B	B	B	B	B	B	B	D	D	D	D	D	B	D	D
Fc ϵ RI γ	B	D	D	.	D	D	B	B	B	B	B	.	B	D	D	D	.	B	B	D	D

^a B = C57BL/6J, D = DBA/2J.

TABLE IV
CXS strain distribution patterns

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Fc γ RII (Ly-17)	S ^a	C	C	S	C	C	S	S	S	C	S	C	S	S
Fc ϵ RI α	S	C	C	S	C	C	S	C	S	C	S	C	S	S
Fc ϵ RI β	S	S	C	S	C	S	S	S	S	S	C	C	C	C

^a S = STS A, C = BALB/cHeA.

TABLE V
AKXL strain distribution patterns

	5	6	7	8	9	12	13	14	16	17	19	21	24	25	28	29	37	38
Ly-10	A	A	A	L	A	.	L	A	L	L	L	L	A	A	A	A	A	L
Ly-1	A	A	A	L	A	A	A	A	L	L	L	L	A	A	L	A	A	L
Fc ϵ RI β	A	A	A	L	A	A	A	A	L	L	L	.	A	L	L	.	A	L

^a A = AKR/J, L = C57L/J.

Figure 5. Homologous regions of Ly-44 and Fc ϵ RI β : Alignment of amino acid sequences. Capital letters in the consensus sequence indicate perfect match. The asterisk indicates a conservative substitution and a dot refers to a sequence mismatch. The residues are numbered according to original publications for Ly-44 (18) and Fc ϵ RI β .

Ly-44	37	54	79	91
	FFMRESKALGAVQIMNGL		YPLWGGIMYIISG	
	FLKKELEFLGATQILVGL		YPFWGAVLFLVLSG	
Fc ϵ RI β	45	63	92	105
Consensus	F*. *E . . . LGA. QI*. GL		YP*WG. *****SG	

pared are 37–129) when a total of three gaps are permitted. Two smaller regions of β (residues 45–62 and residues 92–104) show 50% and 46% identities with the corresponding regions of Ly-44 (residues 37–54 and 79–91, respectively) (Fig. 5). Interestingly, the predicted topology of both molecules is similar with four transmembrane domains and both the amino and carboxy-termini being cytoplasmic. In addition, both have two extracellular N-linked glycosylation sites that appear to be unused (7, 19). However, the limited sequence similarity between β and Ly-44 could represent sequence convergence as opposed to evolutionary duplication

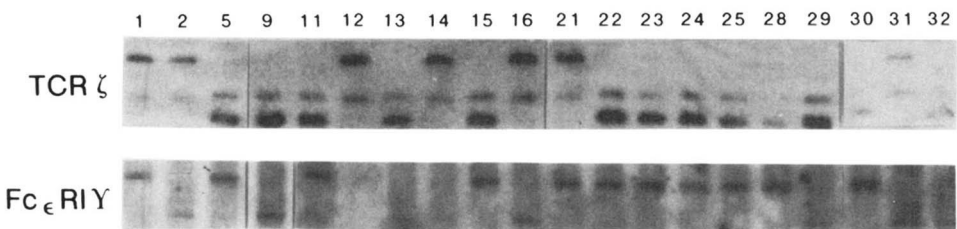
Fc ϵ RI γ is found with Fc γ RII on distal mouse chromosome 1. The inbred strain distribution of Fc ϵ RI γ haplotypes indicated to us that an EcoRI RFLP found between C57BL/6J and DBA/2J mice could generate an SDP in the BXD RI panel (Fig. 6). This SDP for Fc ϵ RI γ displays 17/18 concordancies with Fc γ RII (Ly-17), which has previously been mapped to distal mouse chromosome 1 (9–11, 20). On the basis of one BXD recombinant between Fc ϵ RI γ and Fc γ RII and minimizing the frequency of double crossover, we predict that Fc ϵ RI γ lies approxi-

mately 1.5 cM ($p = 0.985$) distal to Fc γ RII. We have also positioned Fc ϵ RI α distal to Fc γ RII by previous analysis of genetic recombinants in CXS and OXA recombinant inbreds as well as among a backcross panel of mice (C57BL/10N $\times$ SWR/J) $\times$ SWR/J (12). Similarly, we attempted to link Fc ϵ RI γ and Fc ϵ RI α in several common genetic crosses. Despite extensive restriction endonuclease surveys, we were unable to obtain an appropriate RFLP and therefore fail to show a direct genetic comparison of these loci. Preliminary studies by pulsed-field gel electrophoresis have also failed to establish linkage at the molecular level.

It has been noted that Fc ϵ RI γ lacks homology with other FcR but in fact contains considerable relatedness to TCR- ζ chain (2, 21). In addition, the TCR- ζ gene has also been mapped to human chromosome 1 (22), a region syntenic to the distal end of the mouse chromosome 1 (20). We utilized a BamHI RFLP detected with a cDNA probe for TCR- ζ between C57BL/6J and DBA/2J inbred strains with which to follow the SDP in the BXD recombinant inbred panel (Fig. 5). Direct comparison of the TCR- ζ SDP with Fc ϵ RI γ reveals six recombinants among 21 strains

BXD Recombinant Inbred Strains-Chromosome 1

Figure 6. Segregation of polymorphic alleles for TCR- ζ and Fc ϵ RI γ among BXD recombinant inbred mice. Genomic DNA from the BXD individuals listed were digested with BamHI (TCR- ζ) or EcoRI (Fc ϵ RI γ) and hybridized appropriately. Lanes 12 and 14 of Fc ϵ RI γ were visualized on the original autoradiograph.



indicating no apparent genetic linkage between these loci. In addition, TCR- ζ appears to be positioned centromeric to the FcR gene cluster and, in fact, cosegregates within 1.2 cM ($p = 0.997$) of anti-thrombin-3.

DISCUSSION

This report establishes the gene mapping of three subunits of Fc ϵ RI. By genetic recombination, Fc ϵ RI γ and Fc ϵ RII (Ly-17) are closely linked to the distal end of mouse chromosome 1. Fc ϵ RI α and Fc γ RII are also linked in this region of mouse chromosome 1. Both Fc ϵ RI α and Fc ϵ RI γ are likely to be on the distal side of Fc ϵ RII, emphasizing a close association between the three genes. Because γ -chains have no homology with Fc ϵ RI α , Fc γ RII, nor with other FcR (which have also been localized in this region of mouse chromosome 1), it is unlikely that the gene for γ -chains is derived by gene duplication from a precursor common to FcR. It is also possible that the gene for γ -chains is in close proximity to Fc ϵ RI α and Fc γ RII and can be coordinately expressed in different tissues. In an extension of this hypothesis, the genes for γ -chains and for Fc ϵ RI α would be co-expressed in mast cells and basophils, thereby allowing association of their protein products. Correspondingly in macrophages, the genes for γ and Fc γ RIIa—but not for Fc ϵ RI α —may be co-expressed so that γ -chains associate with this Fc γ receptor. β chains, which are found exclusively in Fc ϵ RI, have so far not been shown to be shared by different receptors and therefore would not need to be close to other FcR. Indeed, Fc ϵ RI β is not linked to either of the above genes but to Ly-1 in a region of chromosome 19, which also contains Ly-10 and Ly-44 (CD20).

Interestingly, the human analogs of Ly-44 and Ly-1, CD20 and CD5, respectively, are found as a syntenic unit on human chromosome 11. Thus, the human Fc ϵ RI β subunit may also be found in this region. The chromosomal localization of Fc ϵ RI β directed us to compare Ly-44 and β for limited homologies and other structural similarities. This may indicate that the two genes evolved from a common ancestor. The human analog of Ly-44, the B1 Ag, is a B cell differentiation Ag that plays a role in proliferation as well as differentiation. It will be interesting to investigate whether Ly-44, like β , is associated with other subunits.

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