ment. Whether this regulation is in response to phosphate levels within the macrophage or to other factors is unknown. The second mutant, MS4347, which failed to express a different set of MIPs, is not related to *phoP*. MS4347 is not genetically linked to *phoP* by transductional mapping and expresses normal levels of acid phosphatase, a protein whose expression is controlled by *phoP*. These mutations are located in different genes and regulate a different set of *Salmonella* proteins. Thus, both *phoP*- and non-*phoP*-regulated genes are expressed in response to the macrophage environment.

Heat shock proteins are immunodominant antigens for a number of infectious organisms including *Mycobacterium leprae, M. tuberculosis* (*15*), *Coxiella burnetti* (*16*), *Legionella pneumophilia* (*17*), and *Schistosoma mansoni* (*18*). GroEL is also an immunodominant antigen in *S. typhimurium* infections (*19*). We have now shown that *Salmonella* GroEL and DnaK are induced during infection of macrophages under conditions that do not involve thermoinduction. This suggests a correlation between the abundance of a protein within macrophages and the immunodominance of that protein. Antigen processing takes place within the endosome compartment of antigen-presenting cells (*20*). Processed antigen in combination with MHC molecules (Ia) is presented to T cells in which a specific immune response is stimulated. *Salmonella* remains within the macrophage phagosome or endosomal compartment (*21*), but not all *Salmonella* survive in this hostile environment. Some are killed, as suggested by the initial decrease in viable bacteria (Fig. 1), and degraded; presumably, their proteins are processed and presented on the surface of the macrophage. Our data show that GroEl and DnaK are the most abundant proteins expressed by *Salmonella* within the macrophage; it may be their abundance within an antigen-presenting cell that establishes their immunodominance.

Living attenuated vaccines generally provide better protection than killed vaccines (*22*). This is not merely a consequence of increased bacterial load, but indicates the uniqueness of replicating immunogens in stimulating protective immunity. Our data indicate that bacterial proteins that function as virulence factors are induced within the macrophage, an antigen-processing and antigen-presenting cell. We suggest that a protective response to many pathogens may need to include responses against these same virulence factors. Immunization with living bacteria would generate such a response.

REFERENCES AND NOTES

1. J. F. Miller, J. J. Mekalanos, S. Falkow, *Science* **243**, 916 (1989).
2. C. Nathan, *Trans. R. Soc. Trop. Med. Hyg.* 77, 620 (1983).
3. P. Fields, R. Swanson, C. Haidaris, F. Heffron, *Proc. Natl. Acad. Sci. U.S.A.* **83**, 5189 (1986).
4. C. Lissner, R. Swanson, A. O'Brien, *J. Immunol.* **131**, 3006 (1983).
5. N. Buchmeier and F. Heffron, *Infect. Immun.* **57**, 1 (1989).
6. S. Lindquist and E. Craig, *Annu. Rev. Genet.* **22**, 631 (1988).
7. N. Buchmeier and F. Heffron, unpublished data.
8. ———, unpublished data.
9. R. Morgan, M. Christman, F. Jacobson, G. Storz, B. Ames, *Proc. Natl. Acad. Sci. U.S.A.* **83**, 8059 (1986); Z. Aliabadi, Y. Park, J. Slonczewski, J. Foster, *J. Bacteriol.* **170**, 842 (1988).
10. O. Fayet, T. Ziegelhoffer, C. Georgopoulos, *J. Bacteriol.* **171**, 1379 (1989).
11. S. Hemmingsen *et al.*, *Nature* **333**, 330 (1988).
12. P. I. Fields, E. A. Groisman, F. Heffron, *Science* **243**, 1059 (1989).
13. E. Groisman, E. Chiao, C. Lipps, F. Heffron, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 7077 (1989).
14. S. Miller, A. Kurkal, J. Mekalanos, *ibid.*, p. 5054.
15. D. Young, R. Lathigra, R. Hendrix, D. Sweetser, R. Young, *ibid.* **85**, 4267 (1988); T. Shinnick, M. Vodkin, J. Williams, *Infect. Immun.* **56**, 446 (1988).
16. M. Vodkin and J. Williams, *J. Bacteriol.* **170**, 1227 (1988).
17. P. Hoffman, C. Butler, F. Quinn, *Infect. Immun.* **57**, 1731 (1989).
18. R. Hedstrom, J. Culpepper, R. Harrison, N. Agabian, G. Newport, *J. Exp. Med.* **165**, 1430 (1987).
19. Sera from *S. typhimurium*–immune mice reacted strongly to a 58-kD protein from heat-shocked *Salmonella* by immunoblot analysis (*24*). Sera was from BALB/c mice infected with *S. typhimurium phoP* mutant and then boosted with viable *S. typhimurium* 14028.
20. C. Harding and E. Unanue, *J. Immunol.* **142**, 12 (1989).
21. N. Buchmeier and F. Heffron, unpublished data.
22. R. Germanier, *Infect. Immun.* **5**, 792 (1972).
23. M. Christman, R. Morgan, F. Jacobson, B. Ames, *Cell* **41**, 753 (1985).
24. E. Harlow and D. Lane, in *Antibodies, A Laboratory Manual* (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1988), pp. 490–510.
25. J. Garrels, *Methods Enzymol.* **100**, 411 (1983).

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Organization of the Human and Mouse Low-Affinity FcγR Genes: Duplication and Recombination

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Receptors for immunoglobulin G immune complexes (FcγRII and FcγRIII) are expressed on most hematopoietic cells and show much structural and functional diversity. In order to determine the genetic basis for this diversity, a family of genes encoding the human and mouse receptors was isolated and characterized. Humans have five distinct genes for low-affinity FcγRs, in contrast to two in the mouse. With the use of yeast artificial chromosomes, the genes encoding the human receptors were oriented and linked, which established the structure of this complex locus. Comparison of the human and mouse genes generated a model for the evolutionary amplification of this locus.

WHEN RECEPTORS FOR IMMUNOglobulin G (IgG) are cross-linked by immune complexes, the humoral and cellular immune responses are coupled, and an array of effector and immunomodulatory pathways are triggered (*1*). The molecular basis for the diverse cellular responses initiated by the common ligand, IgG, is being elucidated through the molecular cloning of these IgG receptors (FcγRs). In the human, biochemical and serological studies identified three groups of FcγRs: a high-affinity receptor (FcγRI) and two groups of low-affinity receptors (FcγRII and FcγRIII). Complementary DNA cloning has revealed multiple subtypes within each group (*2–6*). The predicted membrane glycoproteins have similar extracellular domains coupled to divergent transmembrane and cytoplasmic domains. The cell type–specific expression of these molecules has led to the hypothesis that the different cellular responses triggered by IgG immune complexes result from the transduction of different signals through the divergent transmembrane and intracytoplasmic domains of these receptors (*7*). For example, the FcγRIII expressed on natural killer (NK) cells and macrophages (III-2) is a transmembrane protein (*6*) and mediates antibody-dependent cellular cytotoxicity (*8*); a nearly identical molecule (III-1), expressed on granulocytes as a glycosyl phosphatidylinositol (GPI)–linked protein (*5, 6, 9*), cannot. Similarly, the FcγRII proteins mediate different cellular responses on lym-

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phocytes than on myeloid cells. This report addresses the molecular mechanisms that generate the structural diversity resulting in these functional differences.

We compared restriction enzyme digests of human spleen DNA to yeast artificial chromosome (YAC) genomic clones spanning the FcγRIII locus to determine whether our YAC clones contained all of the genes encoding this family of receptors. When Bam HI–digested spleen DNA was hybridized with an FcγRIII probe, two fragments were visible, corresponding to two genes (*6*) (Fig. 1A). These two fragments comigrated with DNA fragments generated by Bam HI digestion of YAC clones spanning this locus (Fig. 1A). Comparison of spleen and YAC DNA with six additional endonucleases always resulted in comigrating fragments. Similarly, when spleen DNA was digested with Hind III and probed with an FcγRII-specific probe, three hybrizing fragments were seen, corresponding to three genes (Fig. 1B). Each of these fragments was found in the YAC clones digested with Hind III. As above, additional enzyme digestions of YAC and spleen DNA always resulted in comigrating fragments. DNA sequence analysis of the genes present on these YAC clones (Table 1) accounted for all known transcripts of FcγRII and FcγRIII (*3–6*). Thus, our data suggest that all members of this gene family have been cloned.

Genomic libraries of human DNA constructed in bacteriophage λ, cosmid, and YAC vectors (*10*) were screened with FcγRII- and FcγRIII-specific probes, mapped with rare cutting restriction enzymes, and aligned (Fig. 2, A and B). Two

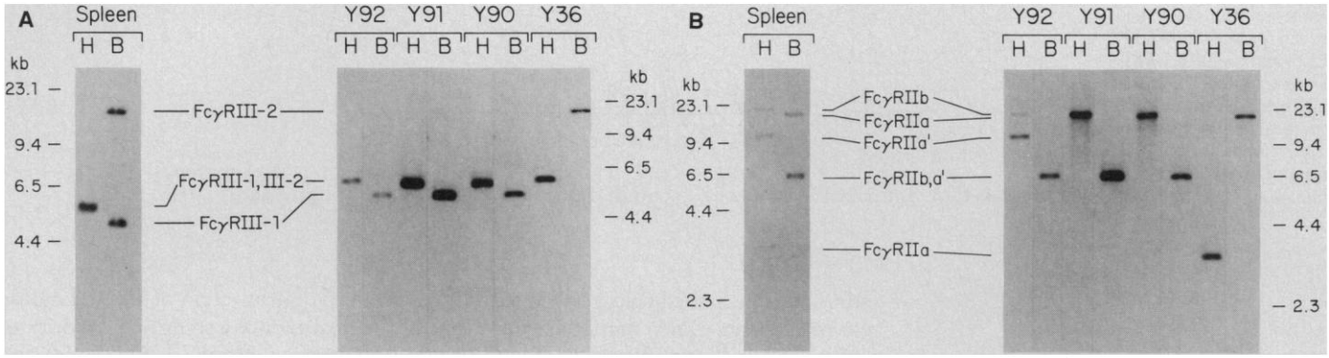

Fig. 1. FcγRII and FcγRIII are encoded by multiple genes in the human genome. Southern blot analysis of human spleen DNA and yeast DNA harboring FcγR artificial chromosomes (YAC) probed for (**A**) FcγRIII and (**B**) FcγRII. Spleen DNA (10 μg) or YAC DNA (2 μg) was digested with the indicated restriction endonuclease, separated on a 1% agarose-tris, acetate, and EDTA gel, transferred to nitrocellulose, and hybridized with either (A) FcγRIII cytoplasmic-3′ untranslated probe [Nco I–Hind III fragment (*6*)] or (B) FcγRII extracellular domain 1 (EC_1) probe [nucleotide 289–370 (*4*)]. The hybridizing fragments are identified with their respective gene, as described in the text. Comparisons between YAC and spleen DNA were performed for a total of eight restriction endonucleases. Comigrating patterns were always observed. B, Bam HI; H, Hind III; Y, YAC clone.

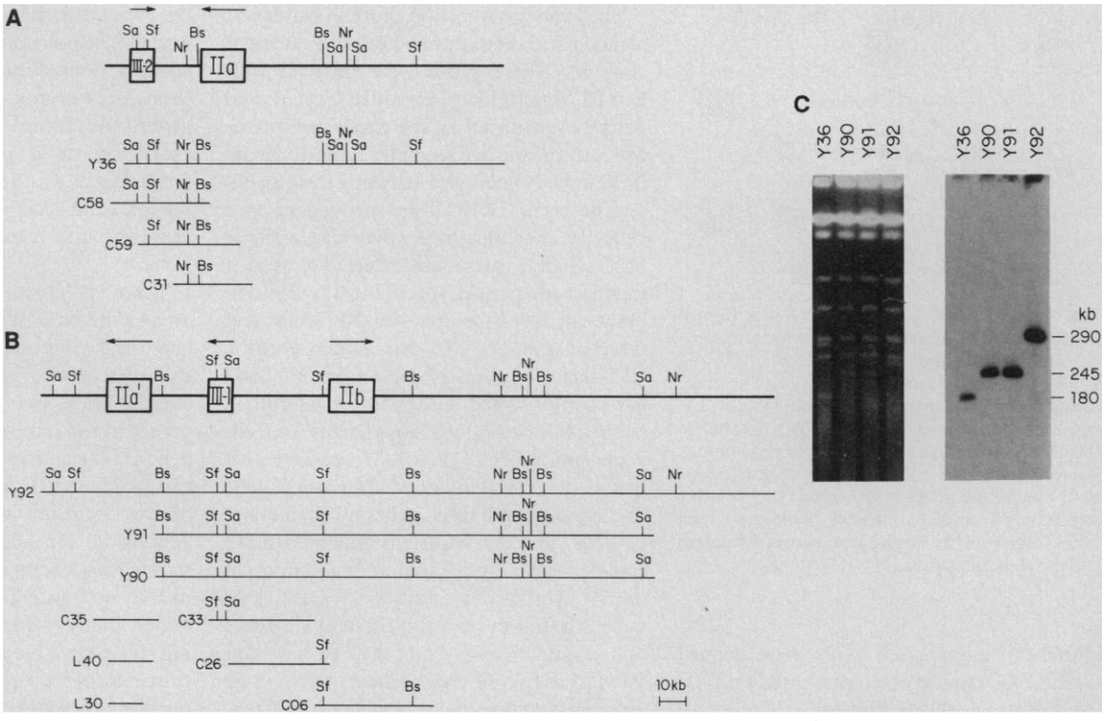

Fig. 2. Structure of the human IgG low-affinity FcR locus. (**A**) and (**B**) Two loci are linked on a single 3.0-Mb Not I fragment. The physical map of each locus indicates the FcγR gene (open rectangle), orientation (overlined arrow), and restriction map. Individual YAC (Y), cosmid (C), or lambda (L) clones corresponding to each locus are indicated. The YAC clones correspond to the Center for Genetics in Medicine numbers as follows: Y36, B2CB; Y90, A249B7; Y91, A249B5; and Y92, A88D10. The identity of each gene was determined by DNA sequence analysis on the indicated clones. The YAC maps were independently confirmed by overlapping cosmid and λ clones for the regions indicated. FcγRIII-1 is the NA-1 allele, with a characteristic Sal I site in extracellular domain 1 (EC_1). Sa, Sal I; Sf, Sfi I; Bs, Bss HII; and Nr, Nru I. (**C**) Southern blot (DNA) analysis of YAC clones isolated for the FcγR locus. Pulsed-field gel separations of four yeast strains harboring YACs (left) were hybridized with an FcγRII probe (right). Y36 and Y92 each contain two YACs, only one of which hybridizes with the FcγR probe.

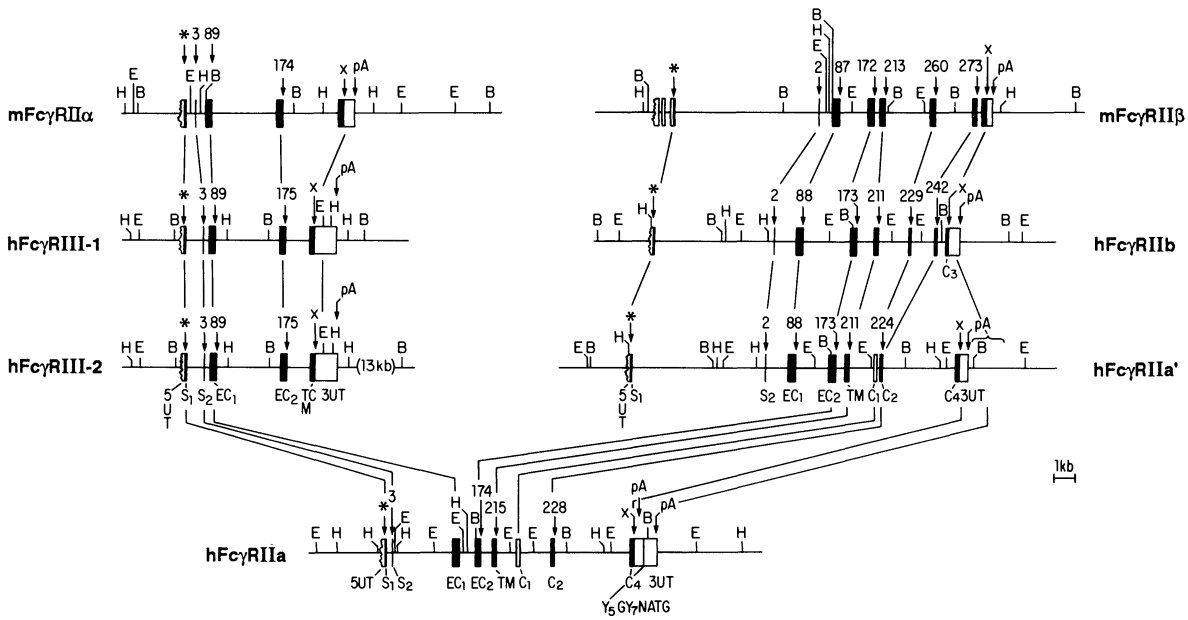

Fig. 3. Structural organization and relation among the FcγR genes. The intron-exon organization for each gene is shown, coding regions are indicated by filled rectangles, transcribed and untranslated regions by open rectangles. Restriction sites in the vicinity of each gene are indicated; the numbers indicate the amino acid preceding the exon-intron junction (see Table 1). Vertical lines connecting exons indicate sequence homology between genes. S, signal; EC, extracellular; TM, transmembrane; C, cytoplasmic; UT, untranslated; pA, polyadenylation site; *, translation initiation; x, translation termination; B, Bam HI; H,Hind III; E, Eco RI. The precise 5′ borders have not been determined, as indicated by the jagged lines.

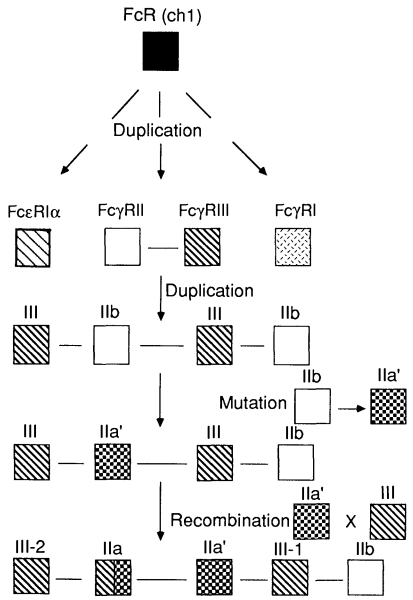

Fig. 4. Model for the evolution of the human FcγR locus. The model is based on the structural characterization and linkage of FcγRII and FcγRIII genes as described in the text. The order of the two loci encoding these genes (Fig. 2) has not been determined, although their reversal to the order shown here would not affect the model. Rectangles denote genes; shading indicates relations among the genes in the locus. The genomic structure of FcεRIα shares homology with FcγRIII genes (*19*). FcγRI gene shows a different structural organization (*20*).

clusters of interspersed genes were defined by the YAC clones, one represented by YAC 36, spanning ≤180 kb and a second, of ≤290 kb, represented by the overlapping YAC clones 90, 91, and 92 (Fig. 2C) (*11*). The distance between these clusters was estimated from pulsed-field gel electrophoresis of human DNA digested with the enzyme Not I. A single fragment of 3.0 Mb hybridizes with FcγRII- and FcγRIII-specific probes (*12*) placing an upper limit of 2.5 Mb separating these clusters. The FcγRII and FcγRIII genes are interspersed in this locus, with III-2 linked to IIa while III-1 is flanked by IIa′ and IIb (Fig. 2, A and B).

The exon organization of these genes was compared to their murine homologs α and β (Fig. 3). These genes were mapped with Eco RI, Bam HI, and Hind III (Fig. 3), and the DNA sequence of the exons and proximal introns was determined (Table 1). From these data, homologies between these genes can be seen. FcγRIII is encoded as two genes in the human (*6*), whereas a single FcγRIII gene (previously referred to as α) is found in the mouse, specifying a transmembrane-anchored protein in NK cells and macrophages (*7, 13*). No evidence for a GPI-anchored form of the murine FcγRIII has been observed, either as a transcript in neutrophils or a phosphatidylinositol-specific phospholipase C (PI-PLC)–sensitive protein (*14*). FcγRII is encoded by the β gene in the mouse and three genes in the human, IIb, IIa′, and IIa. Mouse β and human IIb encode alternatively spliced transcripts of the C1 cytoplasmic exon (*3, 4, 7, 15*). This exon is found in both the IIa′ and IIa genes as a cryptic element (Fig. 3). We have not found a transcript that contains this cryptic exon in polymerase chain reaction (PCR)–amplified cDNA from the RNA isolated from a variety of lymphoid and myeloid sources (*15*). Although IIa′ and IIa share the intron-exon organization of IIb and mouse β, the final exon encoding the majority of the cytoplasmic domain is distinct (*4*) and predicts a protein with a divergent intracytoplasmic domain. The origin of the novel cytoplasmic domain for IIa is suggested from these studies to be the result of the evolutionary divergence of this final cytoplasmic exon. The exon in IIb and β is apparent within this larger exon, bordered by a mutated splice acceptor site. A single nucleotide insertion in this sequence resulted in a nonfunctional splice acceptor site (Fig. 3). A cryptic site upstream is utilized instead, resulting in a novel cytoplasmic exon for these genes. Finally, because FcγRIIa has sequence homologies to both the α/III and β/IIb genes, this gene probably arose through recombination or gene conversion.

There is much sequence redundancy among the FcγRII genes. For example, IIa′ and IIa encode mature proteins with 96% overall sequence identity throughout their length. These two genes are expressed together in the same cell types (*4*), thus, both gene products may not be essential for normal function. Consistent with this idea is the observed allelism we have found for IIa′. Among all IIa′ clones, 75% have a TAG termination codon in place of a CAG codon in EC_1 and an AT in place of a GT splice donor after the first cytoplasmic exon, making this gene a pseudogene. To rule out the existence of two genes encoding these sequence differences, DNA and RNA were isolated from the granulocytes of four individuals and characterized by PCR with primers that specifically amplify the IIa′

gene. Of the four individuals, two were heterozygous, one was homozygous for the pseudogene, and one was homozygous for the functional gene.

The structural analysis presented above suggests a scheme for the evolutionary amplification of the human locus (Fig. 4). Chromosome in situ hybridization and analysis of mouse-human hybrids have placed the genes for FcγRII, FcγRIII, FcγRI, and FcεRIα on the long arm of chromosome 1, band q23–24 (*17*). This region of chromosome 1 is syntenic in the mouse for these and other markers (*18*). Perhaps after duplication and divergence of an ancestral FcR gene on chromosome 1, the low-affinity IgG FcRs underwent further duplication and divergence into an FcγRII-like and FcγRIII-like gene. In the mouse, no further duplication occurred, whereas in the human, duplication of this FcγRII and FcγRIII locus most likely occurred. Mutation of the IIb splice acceptor sequence could give rise to IIa′, and recombination or gene conversion between IIa′ and III could result in a fifth gene, IIa. The sequence data is consistent with this model, indicating a rank order of similarity of IIb > IIa′ > IIa to mouse β.

The complex functional diversity mediated by receptors for IgG immune complexes is mirrored in the genetic complexity of the locus that encodes these genes. Our analysis will facilitate the dissection of the regulation of these genes and their role in pathological states. The linkage of these FcRs with FcRs mediating different isotype specificities and affinities for ligand suggests that this region of chromosome 1 may represent a conserved linkage group for Fc binding.

Table 1. Comparison of the sequences at the intron-exon borders for FcγRII and FcγRIII. The nucleotide sequences at the intron-exon borders for each gene shown in Fig. 3 are presented and numbered accordingly.

Gene	Exon	5′border	3′border	Amino acid
β	1($5UT_1$-$5UT_2$)	GAT GGT Ggtaagt-----catcctccatcacagAC	TGA GGC	
β	2($5UT_2$-$5UT/S_1$)	TAT TCT Ggtaagt-----gtactatctgccaagCC	GGG AGG	
β	3($5UT/S_1$-S_2)	GTG CTA Agtaagt-----cttcctttctttcagAT	CTT GCT	Asn(-5)
IIb	1($5UT/S_1$-S_2)	TTC CTG Ggtgagt-----ctttctgtcttacagCT	CCT GTT	Ala(-5)
IIa′	1($5UT/S_1$-S_2)	TTC CTG Ggtgagt-----ctttctgtcttacagCT	CCT GTT	Ala(-5)
IIa	1($5UT/S_1$-S_2)	CTG CTG Ggtgagt-----tcttctctttttacagCT	TCT GCA	Ala(-4)
β	4(S_2-EC_1)	ACT CAT Ggtgagt-----tccaaaattgagcagAT	CTT CCA	Asp(+3)
IIb	2(S_2-EC_1)	ACA CCT Ggtaagt-----ctctctgcccctcagCA	GCT CCC	Ala(+3)
IIa′	2(S_2-EC_1)	ACA CCT Ggtaagt-----ctctctgcccctcagCA	GCT CCC	Ala(+3)
IIa	2(S_2-EC_1)	CAA GCT Ggtgagt-----cactctgcccctcagCA	GCT CCC	Ala(+4)
β	5(EC_1-EC_2)	ATT TCT Ggttagt-----tttcgtgtctttcagAC	TGG CTG	Asp(+88)
IIb	3(EC_1-EC_2)	CTT TCT Ggtcagt-----ttttgtgtctttcagAG	TGG CTG	Glu(+89)
IIa′	3(EC_1-EC_2)	CTT TCT Ggtcagt-----tttctgtgctttcagAG	TGG CTG	Glu(+89)
IIa	3(EC_1-EC_2)	CTT TCC Ggtcagt-----atttgtgtctttcagAA	TGG CTG	Glu(+90)
β	6(EC_2-TM)	GTC CAA Ggtaagt-----gtctgtcttctccagGG	CCC AAG	Gly(+173)
IIb	4(EC_2-TM)	GTC CAA Ggttatg-----gtctgtcttccctagCT	CCC AGC	Ala(+174)
IIa′	4(EC_2-TM)	GTC CAA Ggtatgg-----gtctgtcttccctagCT	CCC AGC	Ala(+174)
IIa	4(EC_2-TM)	GTC CAA Ggtatgg-----gtctgtcttccctagTG	CCC AGC	Val(+175)
β	7(TM-C_1)	GTT CCA Ggttggt-----acgtgcccctcctagCT	CTC CCA	Ala(+214)
IIb	5(TM-C_1)	ATT TCA Ggtttgt-----gtgtgcccctcccagCT	CTC CCA	Ala(+212)
IIa′	5(TM-C_1)	ATT TCA Ggtttgt----[gtgtgaccctcccagCT	CTC TCA	*
IIa	5(TM-C_1)	ATT TCA Ggtttgt----[gtgtgtccctcccagCT	CTC CCA	*
β	8(C_1-C_2)	AGC CCA Tgtgagt-----tattttcatccacagAC	AAT CCT	Tyr(+260)
IIb	6(C_1-C_2)	AAA CCA Ggtgagt-----ttctttttcccacagCC	AAT CCC	Ala(+230)
IIa′	6(C_1-C_2)	AAA CCA Ggtgagt]----tctttttcccacagCC	AAT TCC	Ala(+212)
IIa	6(C_1-C_2)	AAA CCA Ggtgaat]----tctttttcccacagCC	AAT TCC	Ala(+216)
β	9(C_2-C_3)	ACT GAG gtgagg-----ttctgctttccctag	GCT GAG	Glu(+272)**
IIb	7(C_2-C_3)	GTT GGG gtgagt-----ttctgccttctctag	GCT GAG	Gly(+242)
IIa′	7(C_2-C_4)	TTT GAG gtgagt-----aaatctttcctgcag	CCA CCT	Glu(+224)
IIa	7(C_2-C_4)	TTT GAG gtgagt-----aatgctttcctgcag	CCA CCT	Glu(+228)
α	1($5UT/S_1$-S_2)	CTG TTT Ggtgagt-----ctttcttctttacagCT	TTT GCA	Ala(-4)
III-1	1($5UT/S_1$-S_2)	CTT CTA Ggtaagt-----tctttttttcttgcagTT	TCA GCT	Val(-4)
III-2	1($5UT/S_1$-S_2)	CTT CTA Ggtaagt-----tctttttttcttgcagTT	TCA GCT	Val(-4)
α	2(S_2-EC_1)	CAG AGT Ggtaagt-----ttctctcactctcagCA	GCT CTT	Ala(+4)
III-1	2(S_2-EC_1)	CGG ACT Ggtgagt-----atcttggctcctcagAA	GAT CTC	Glu(+4)
III-2	2(S_2-EC_1)	CGG ACT Ggtgagt-----atcttggctcctcagAA	GAT CTC	Glu(+4)
α	3(EC_1-EC_2)	ATT TCT Ggttagt-----ctttagttctttcagAC	TGG CTG	Asp(+90)
III-1	3(EC_1-EC_2)	CAT GTC Ggtgagt-----ctctgtgtctttcagGC	TGG CTG	Gly(+90)
III-2	3(EC_1-EC_2)	CAT GTC Ggtgagt-----gtctgtgtctttcagGC	TGG CTG	Gly(+90)
α	4(EC_2-TM/C)	GTC CAA Ggtgagc-----cctcctcccttccagAT	CCA GCA	Asp(+175)
III-1	4(EC_2-TM/C)	ACT CAA Ggtgaga-----cacttctcctaatagGT	TTG GCA	Gly(+175)
III-2	4(EC_2-TM/C)	ACT CAA Ggtgaga-----acttctccctaatagGT	TTG GCA	Gly(+175)

*No transcripts have been identified that contain this exon, although an open reading frame is maintained. **The intron-exon border occurs between two codons, the 5′ of which is indicated.

REFERENCES AND NOTES

1. J. V. Ravetch and C. L. Anderson, in *Fc Receptors and the Action of Antibodies*, H. Metzger, Ed. (American Society for Microbiology, Washington, DC, 1989), pp. 211–235, J.-P. Kinet, *Cell* **57**, 351 (1989); J. C. Unkeless, E. Scigliano, V. H. Freedman, *Annu. Rev. Immunol.* **6**, 251 (1988).
2. J. M. Allen and B. Seed, *Science* **243**, 378 (1989); *Nucleic Acids Res.* **16**, 1184 (1989).
3. S. G. Stuart *et al.*, *J. Exp. Med.* **166**, 1668 (1988); M. L. Hibbs *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **85**, 2240 (1988); S. Stengelin, I. Stamenkovic, B. Seed, *EMBO J.* **7**, 1053 (1988); S. G. Stuart *et al.*, *ibid.* **8**, 3657 (1989).
4. D. G. Brooks, W. Q. Qiu, A. D. Luster, J. V. Ravetch, *J. Exp. Med.* **170**, 1369 (1989).
5. D. Simmons and B. Seed, *Nature* **333**, 568 (1988); G. A. Peltz *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 1013 (1989); B. J. Scallon *et al.*, *ibid.*, p. 5079.
6. J. V. Ravetch and B. Ferussia, *J. Exp. Med.* **170**, 48 (1989).
7. J. V. Ravetch *et al.*, *Science* **234**, 718 (1986).
8. B. Perussia and J. V. Ravetch, in preparation.
9. P. Selvaraj, W. F. Rosse, R. Silber, T. A. Springer, *Nature* **333**, 565 (1988); T. W. J. Huizinga *et al.*, *ibid.*, p. 667.
10. D. T. Burke, G. F. Carle, M. V. Olson, *Science* **236**, 806 (1987); B. H. Brownstein *et al.*, *ibid.* **244**, 1348 (1989).
11. Pulsed-field gel analysis was performed on a Bio-Rad CHEF DR-II apparatus, using 1% LE agarose gel, 0.5× tris-borate EDTA buffer at 14°C, with a ramped pulse from 20 to 50 s over 24 hours at 180 V. The DNA was nicked by ultraviolet light for 60 s, before transfer to nitrocellulose. The membrane was then probed with a nick-translated fragment specific for various human FcγR genes.
12. Fourteen rare cutting restriction enzymes were used to map this locus by pulsed-field gel analysis. All gave multiple fragments with either FcγRII or FcγRIII probes with the exception of Not I.
13. B. Perussia *et al.*, *J. Exp. Med.* **170**, 73 (1989).
14. J. V. Ravetch and B. Perussia, unpublished observations.
15. V. A. Lewis, R. Koch, H. Plutner, I. Mellman, *Nature* **324**, 372 (1986); M. L. Hibbs *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **83**, 6980 (1986).
16. D. Brooks and J. V. Ravetch, unpublished observations.
17. H. O. Grundy *et al.*, *Immunogenetics* **29**, 331 (1989); K. Huppi, B. A. Mock, J. Hilgers, J. Kochan, J.-P. Kinet, *J. Immunol.* **141**, 2807 (1988); J. V. Ravetch, unpublished observations.
18. M. F. Seldin, H. C. Morse R. C. LeBoeuf, A. D. Steinberg, *Genomics* **2**, 48 (1988).
19. I. Tepler, A. Shimiju, P. Leder, *J. Biol. Chem.* **264**, 5912 (1989); C. Ra, H.-H. E. Jouvin, J.-P. Kinet, *ibid.*, p. 15323.
20. R. Pearse and J. V. Ravetch, unpublished observations.

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