Analysis of part of the chicken Rfp-Y region reveals two novel lectin genes, the first complete genomic sequence of a class I -chain gene, a truncated class II -chain gene, and a large CR1 repeat

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Sally Rogers · Iain Shaw · Norman Ross · Venugopal Nair · Lisa Rothwell · Jim Kaufman · Pete Kaiser

Analysis of part of the chicken *Rfp-Y* region reveals two novel lectin genes, the first complete genomic sequence of a class I α-chain gene, a truncated class II β-chain gene, and a large CR1 repeat

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Abstract The *Rfp-Y* region lies on the same microchromosome as the B-F/B-L region of the B complex, yet in contrast to the latter it is poorly characterised. To date it has been shown to contain at least two class I α-chain (*Y-F*) genes, a class II B-chain gene and a C-type lectin-like gene. We describe the sequencing and analysis of some 20 kb of the *Rfp-Y* region, and identify several new genes. These include two novel C-type lectin-like genes (*Y-Lec1* and *Y-Lec2*) that differ strongly from the previously described C-type lectin-like gene found in the *Rfp-Y* region. We describe a complete genomic sequence of a class I α-chain (*Y-F*) gene and its promoter from the *Rfp-Y* region. The predicted cDNA from this gene has high homology to the previously reported *Y-F* cDNAs. The promoter contains an altered enhancer A element. This portion of the *Rfp-Y* region also contains a truncated class II B-chain (*Y-LB*) gene, as well as a large chicken repeat 1 (CR1) element.

Keywords Chicken · Class I · Class II · Lectin · *Rfp-Y*

Introduction

There are two groups of class I α-chain and class II β-chain genes on chicken microchromosome 16 (Bloom and Bacon 1985; Guillemot et al. 1988; Fillon et al. 1996; Miller et al. 1996), the B complex (Briles et al. 1957; Miller et al. 1994a) and the *Rfp-Y* region system (Briles et al. 1993; Miller et al. 1994b), which are unlinked in genetic crosses.

The B complex contains the B-F/B-L region, which is the chicken major histocompatability complex (*MHC*). It contains classical class I α-chain (*B-F*) and class II β-chain (*B-LB*) genes, and determines rapid allograft rejection, mixed lymphocyte reactions and resistance to a variety of infectious pathogens. In particular, many studies show that the B region confers striking resistance or susceptibility to Marek's disease virus (MDV), an oncogenic α-herpesvirus (Calnek 1985; Schat 1987; Dietert et al. 1990; Schat et al. 1994). In total, the B-F/B-L region contains 19 genes in 92 kb of DNA, including two C-type lectin-like genes (Kaufman et al. 1999a). Both of these genes encode predicted type II transmembrane proteins, one with an apparent immunoreceptor tyrosine-based inhibitory motif (ITIM) in the amino-terminal cytoplasmic tail, the other with an apparent endocytosis motif (S. Rogers, unpublished data). One predicted protein is closely related to lectin-like natural killer receptors and is expressed in chicken NK cell lines but not T, B and macrophage cell lines (Kaufman et al. 1999b).

The *Rfp-Y* region does not determine any of the immunological phenomena listed above, although Pharr et al. (1996) did demonstrate that *Rfp-Y* participates in allograft rejection. The number of loci in the *Rfp-Y* system is unclear, and nomenclature is not established beyond the use of *Y-F* for all class I α-chain genes in this region. The *Y-F* molecules contain distinct substitutions in residues that are highly conserved in the peptide-binding groove of classical molecules (Afanassieff et al. 2000). It is therefore highly unlikely that the *Y-F* encoded molecules are capable of presenting antigen in a manner similar to classical class I molecules, and they can be considered as

S. Rogers · I. Shaw · N. Ross · V. Nair · L. Rothwell · J. Kaufman · P. Kaiser (✉)
Institute for Animal Health,
Compton, Berkshire, RG20 7NN, UK
e-mail: pete.kaiser@bbsrc.ac.uk
Tel.: +44-1635-577277
Fax: +44-1635-577263

Present address:
I. Shaw, Immunodiagnostics Laboratory,
National Diagnostics Centre,
National University of Ireland,
Galway, Eire

non-classical. In addition, there is at least one class II B-chain (*Y-LB*) gene, which is not polymorphic (Zoorob et al. 1990; 1993). Also, one C-type lectin gene has been described (Bernot et al. 1994). The function of the *Rfp-Y* MHC genes and their association, if any, with disease are unclear. There are conflicting reports of *Rfp-Y* MHC genes associating with resistance to Marek's disease (Wakenell et al. 1996; Vallejo et al. 1997; Lakshmanan and Lamont 1998), and one report of an association between *Rfp-Y* genotype and the fate of Rous sarcomas (LePage et al. 2000).

Materials and methods

Construction of MDV cosmids

An ordered series of MDV cosmids were constructed. Briefly, chick embryo fibroblasts from HPRS-RIR (Houghton Poultry Research Station-Rhode Island Red; an outbred line imported into the United Kingdom in 1961 from a commercial breeder, and since bred as a closed flock under SPF conditions) birds were infected with the RB1B strain (Schat et al. 1982) of MDV. Viral DNA was extracted from purified virus particles according to the method of Lee et al. (1982). A partial *Mbo*I digest of the viral DNA yielded 30–40 kb DNA fragments, which were isolated by electroelution and cloned into the *Bam*HI site of the cosmid vector pWE15. The resulting colonies were screened by hybridisation to known MDV genes, and overlapping fragments identified by restriction endonuclease analysis and hybridisation.

Sequencing and analysis

Cosmid DNA was isolated by standard methods (Sambrook et al. 1989). One of the cosmids, 2E2, was commercially sequenced (LARK Technologies). The complete sequence of the cosmid was determined on each strand. Sequence data were analysed with the Wisconsin Package software (Genetics Computer Group; Devereux et al. 1984). The sequence of the *Rfp-Y* regions of 2E2 has been deposited in the EMBL database with accession number AJ277927.

Construction of phylogenetic trees

Amino acid sequences were aligned using the CLUSTAL W program (Thompson et al. 1994). The resulting alignments were then adjusted by eye to maximise sequence similarity. Analysis used the PHYLIP program in GCG9 (Genetics Computer Group; Devereux et al. 1984). Trees were constructed using the Neighbor-Joining method; the algorithm being that of Saitou and Nei (1987), simplified by Studier and Keppler (1988) and modified by Swofford et al. (1996).

Results and discussion

Identification of *Rfp-Y* region genomic sequence in cosmid 2E2

We sequenced a cosmid (2E2) containing DNA isolated from MDV-infected (RB1B strain of MDV) chick embryo fibroblasts (CEF), isolated from an outbred line of chickens (HPRS-RIR). Sequence analysis showed the cosmid to be chimaeric, containing a large region (approximately 20 kb) of chicken genomic DNA corresponding to the *Rfp-Y* region, joined at an *Mbo*I restriction site to MDV-specific sequences from the UL region of the MDV genome (data not shown). The cosmid was sequenced commercially on both strands, and the *Rfp-Y* sequence has been deposited in the EMBL database with accession number AJ277927.

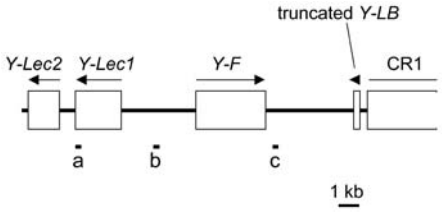


Fig. 1 Gene order (*open boxes*) in the sequenced region of the *Rfp-Y* region from outbred RIR chickens. *Arrows* indicate transcriptional orientation. *Solid bars a–c* indicate non-coding regions of this sequenced region of the *Rfp-Y* which have identity with sequences 3′ to the published *Y-FV* gene and *Y-FVI* pseudogene (Afanassieff et al. 2001). Regions *a* and *b* have identity with the 3′*UTR* of *Y-FVI*, *c* with the 3′*UTR* of *Y-FV*; *a* (nt 2981–3160) is in the 3′*UTR* of *Y-Lec1* before the polyA site, *b* (nt 5988–6146) in the intergenic region between *Y-Lec1* and *Y-F*, and *c* (nt 11730–11910) after the polyA site in the 3′*UTR* of *Y-F*

Figure 1 shows the genes found in this part of the *Rfp-Y* region, and their transcriptional orientations. At least 3,300 nucleotides (nt) of the *Rfp-Y* region genomic DNA consists of a chicken repeat 1 (CR1) element. As well as the genes identified, there are also non-coding sequences (Fig. 1) in this part of the *Rfp-Y* region that have identity with sequences 3′ to the published *Y-FV* gene and *Y-FVI* pseudogene (Afanassieff et al. 2001).

The *Rfp-Y* region contains at least two C-type lectin-like genes

Figure 2 shows the nt and predicted amino acid (aa) sequences of the two C-type lectin-like genes (*Y-Lec1* and *Y-Lec2*) found in this area of the *Rfp-Y* region—the first full-length C-type lectin-like genes characterised in the *Rfp-Y* region. Each gene consists of five exons and four introns. Downstream of *Y-Lec1* is both a non-canonical (CATAAA) and canonical (AATAAA) polyadenylation signal, whereas downstream of *Y-Lec2* there is only a non-canonical polyadenylation signal (CATAAA) (all shown in *bold* in Fig. 2). Both Y-Lec1 and Y-Lec2 are predicted to be type II membrane proteins, since they lack signal peptides, contain a single hydrophobic transmembrane region and are therefore presumably orientated with their carboxy-termini outside of the cell and their amino-termini in the cytoplasm.

Figure 3 shows an alignment of the C-type lectin-like domains of Y-Lec1 and Y-Lec2 with those of other C-type lectins, including ch17.5, a previously identified C-type lectin encoded by the *Rfp-Y* region (Bernot et al. 1994). Neither Y-Lec1 nor Y-Lec2 contains any obvious intracellular signalling motifs, as found in inhibitory lectin-like receptors (reviewed in Long 1999). The

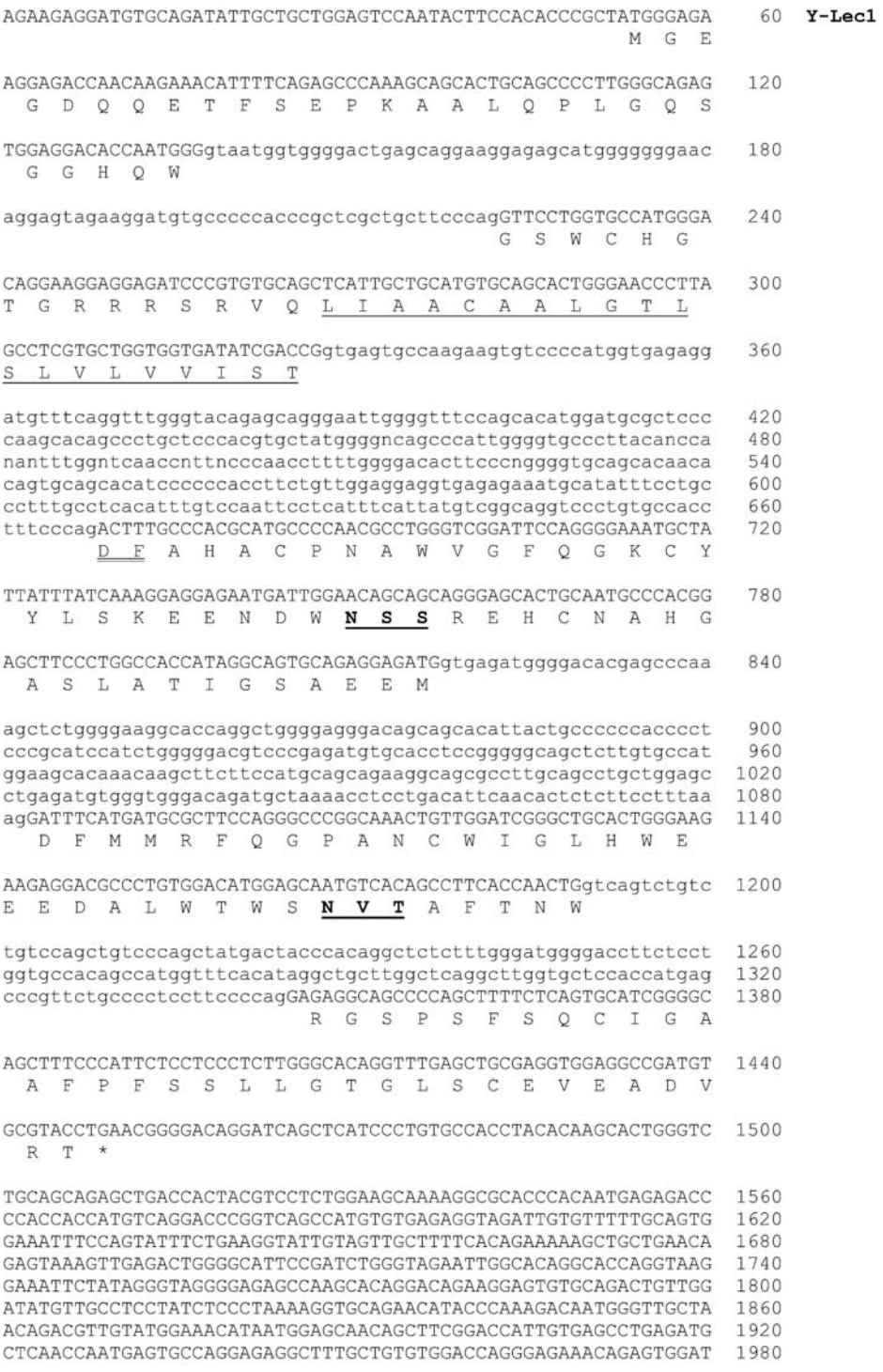
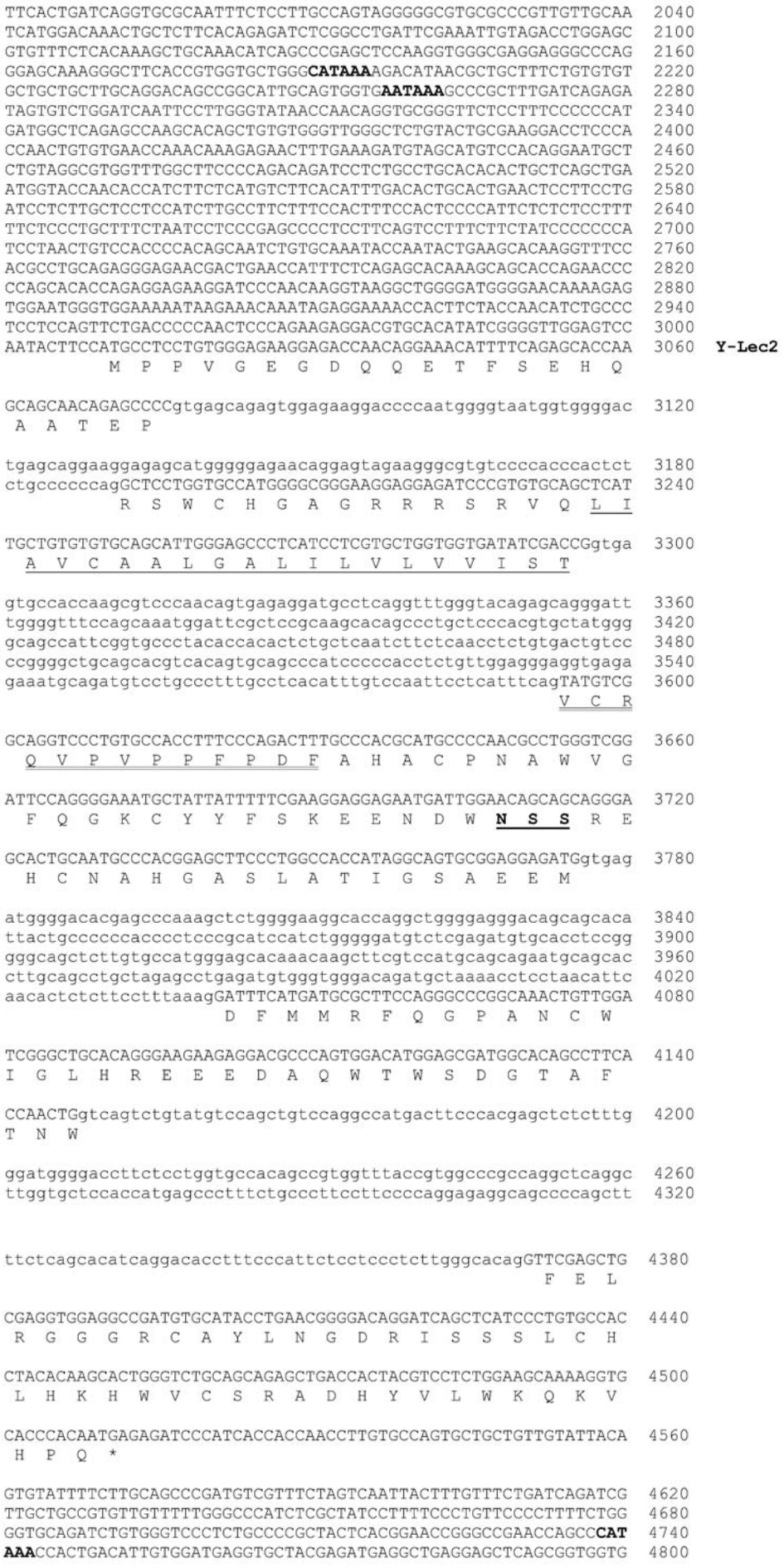


Fig. 2 Complete nucleotide sequence showing the structure of the *Y-Lec* genes. Nucleotides are numbered arbitrarily from upstream of *Y-Lec1*. The predicted aa sequences of the coding regions (as assigned from the cDNA) are shown below the nt sequence. *Lowercase letters* in the nt sequence indicate intron sequences. Potential polyadenylation signals in the 3′*UTR* of the two genes are shown *bold*. Potential N-glycosylation sites are shown *underlined in bold*. The potential transmembrane regions in the protein are *underlined*. The potential stalk regions are *double underlined*

absence of charged residues in their transmembrane domains (Fig. 2) suggests that they do not associate with signalling adaptors such as DAP12 (Smith et al. 1998). Both lectins seem to lack aa residues shown to be important for calcium-dependent binding of carbohydrates by human mannose binding protein (reviewed in Weis et al. 1998) (see Fig. 3). Y-Lec1 has two potential N-glycosylation sites and a very short stalk (Fig. 2). Y-Lec2 has a single potential N-glycosylation site and a longer stalk than Y-Lec1 (Fig. 2), very similar to the stalk region of chB-Lec (data not shown). The vast majority of C-type lectins contain four cysteines that are involved in intrachain disulphide bond formation. All four cysteines are present in Y-Lec2, but Y-Lec1 lacks the carboxy-terminal cysteine. The effect of this missing cysteine on the three-dimensional structure, and thus on the expres-

Fig. 2 (continued)



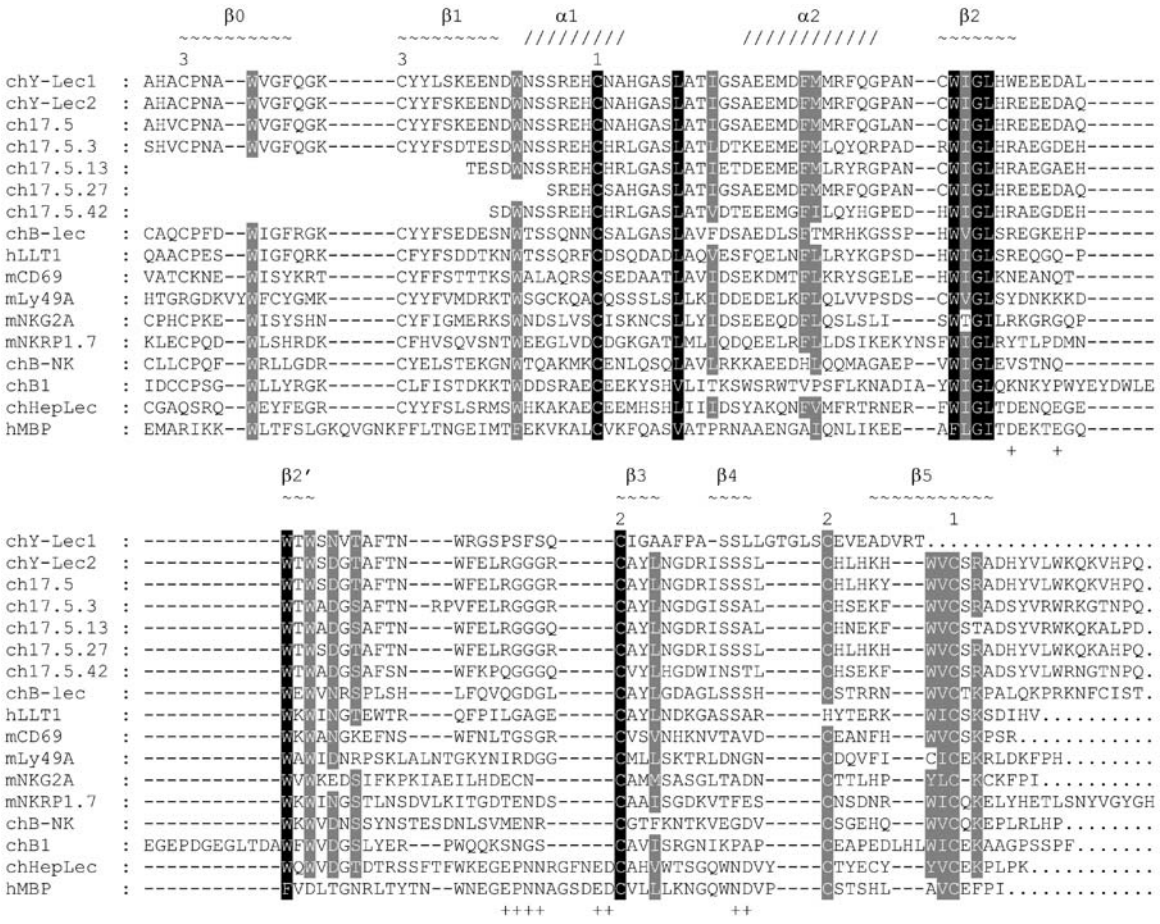


Fig. 3 Alignment of C-type lectin-like domains of Y-Lec1 and Y-Lec2 with those of other C-type lectins. Residues strictly conserved among C-type lectins are shown in *white on black*, similar residues are shown in *white on grey*. *Dashes* denote gaps introduced for optimal alignment. *Numbering above the alignment* indicates conserved cysteine residue pairs involved in disulphide bonds — those marked *1* and *2* are conserved in the vast majority of C-type lectins, those marked *3* are found only in long-form C-type lectin domains. The secondary structure elements of mouse Ly-49A (Tormo et al. 1999) are indicated above the alignment: *wavy dashes* (~~) denote β-strands and *slashes* (*//*) denote α-helices. Residues involved in calcium-dependent binding of carbohydrates by human mannose binding protein (hMBP) are indicated *below the alignment* (+). Accession numbers used are as follows: chicken 17.5 lectin (Q90636), chicken B-Lec and chicken B-NK (AL023516), chicken bursal lectin B1 (Q90644), mouse Ly-49A (P20937), mouse NKG2A (Q9Z202), mouse NKR-P1.7 (P27811), mouse CD69 (P37217), human LLT1 (Q9UHP7), chicken hepatic lectin (chhe-plec) (P02707) and human MBP (P11226). All other ch17.5 sequences are from Bernot et al. (1994) (*ch* chicken; *m* mouse; *h* human)

sion and function of Y-Lec1 protein, is unknown. Human LLT1 also lacks one of the four conserved cysteines, yet is expressed on the surface of human NK, T, and B cells (Boles et al. 1999).

Phylogenetic analysis of C-type lectin genes (Fig. 4) demonstrates that *Y-Lec1* and *Y-Lec2*, together with the previously reported lectin sequences (Bernot et al. 1994), form three distinct groups—ch17.5.3, ch17.5.13 and ch17.5.42 in one group, chY-Lec2, ch17.5 and ch17.5.27 in a second group, and chY-Lec1 alone in the third. This may suggest that the *Rfp-Y* region contains at least three C-type lectin families, two of which have several alleles or loci. However, there is no direct evidence that the ch17.5.3, ch17.5.13 and ch17.5.42 cDNAs are actually encoded within the *Rfp-Y* region.

The *Rfp-Y* region contains at least two *Y-F* genes, one of which has an altered enhancer A element in its promoter

Comparison of the structure and sequence of the *Y-F* gene described here with a published *Y-F* gene (Afanassieff et al. 2001) shows that the coding sequences of the genes are similar (95.0% nt and 94.3% aa identity) but by no means identical, with slightly different intron lengths (data not shown). It is possible that different *Rfp-Y* haplotypes contain different *Y-F* genes.

The 3′ region of the new *Y-F* gene contains a single canonical polyadenylation site, 870 nt from the stop codon (data not shown). The 3′ region of the published *Y-F* gene contains a single canonical polyadenylation site 119 nt from the stop codon (Afanassieff et al. 2001). The 3′ region of the *B-F* gene (Kroemer et al. 1990) contains

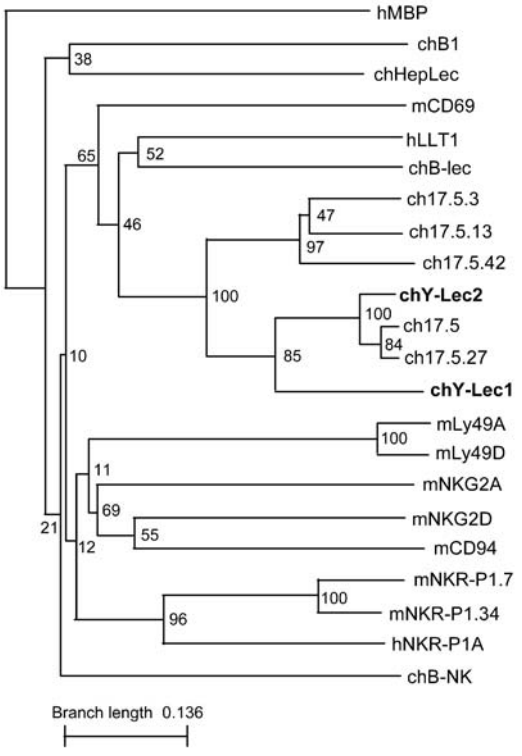


Fig. 4 Unrooted phylogenetic tree of C-type lectins, based on the aa sequences shown in Fig. 3. Sequences used were from the beginning of β-strand 0 (β0) to the end of β-strand 5 (β5), omitting the highly variable sequences after β5. *Numbers* indicate bootstrap values from 500 replicates. For the branch lengths, the distance given in the scale represents 0.136 aa substitutions per site. Accession numbers are as in Fig. 3, with the addition of mouse Ly-49D (Q60651), mouse NKG2D (AF054819), mouse CD94 (AF057714), human NKR-P1A (U11276) and mouse NKR-P1.34 (P27812). All ch17.5 sequences are from Bernot et al. (1994)

two canonical polyadenylation sites, 145 nt and 686 nt from the stop codon, respectively.

To the best of our knowledge, this is the first published report of a *Y-F* gene sequence including the promoter. Within the promoter of this *Y-F* gene (Fig. 5) we could clearly identify only some of the regulatory elements identified by Kroemer et al. (1990) in the promoter of a *B-F* gene. Figure 5 shows a comparison of the regulatory elements of the promoters of the *B-F* gene, a *Y-F* gene in the databases (*YFV*; accession no. AF218783) and the *Y-F* gene described in this project. Of the two transcription initiation sites identified by Kroemer et al. (1990) in the *B-F* gene promoter, neither is conserved in the *Y-F* promoters. The *Y-F* gene promoter contains, in order (with increasing distance from the transcriptional start-point), an Sp1 box, a CAAT box, a Y box, and an X/X2 box. The *YFV* promoter shares these regulatory elements, but the available sequence ends upstream of the X/X2 box. The two *Y-F* promoters overlap by 129 nt, and share 80.6% nt identity, suggesting that they are separate genes. Upstream of the X/X2 box the *B-F* and *Y-F* promoter sequences diverge, and the other elements identified in the *B-F* promoter—the S/W box, interferon response element (IRE) and the so-called enhancer A element (an NF-κB binding site)—are less conserved.

The S/W box has only 5/7-nt identity between the two promoters. There is, however, another apparent S/W box (GGAGCCT — 6/7-nt identity with a mammalian class II S/W box — Riegert et al. 1996; van den Elsen et al. 1998) upstream in the *Y-F* promoter (226 nt upstream of the X box) not present in the *B-F* promoter (data not shown).

The IRE in the *B-F* promoter has been shown to be functional in the induction of chicken MHC class I gene expression by chicken interferon (Zoller et al. 1992). The equivalent region of the *Y-F* promoter is diverged (7/10-nt identity, with a 2-nt insertion in the *Y-F* promoter), suggesting that the *Y-F* gene product might not be induced by interferon. However, the *Y-F* promoter, where it aligns with the *B-F* IRE element, has the motif TTTCACTT (Fig. 5). This motif is a perfect class I α-chain gene promoter IRE sequence compared, for example, with the mouse H-2Ld sequence (Shirayoshi et al. 1988). There is also an alternative potential IRE element (TTTCGCTTTCA) slightly upstream in the *Y-F* promoter.

The enhancer A element is the most important element for transcription of mammalian class I α-chain genes (Kimura et al. 1986; Gobin et al. 1998). It is, in fact, an NF-κB binding site, with two motifs to bind NF-κB family member dimers (reviewed in David-Watine et al. 1990). In the chicken classical class I loci, the *B-F1* (minor) region has a disrupted or absent enhancer A and produces far less mRNA than the *B-F2* (major) region, which has an intact enhancer A (Kaufman et al. 1999a, 1999b). The *Y-F* promoter enhancer A element has limited identity (12/17 nt), and there is a 2-nt insertion between the two binding motifs, putting them out of phase. Given this spatial rearrangement, it seems unlikely that the normal cellular transcription mechanisms will transcribe the two gene products with the same efficiency. However, the sequence may still fit the criteria for a minimal NF-κB binding site (Dey et al. 1992; Giuliani et al. 1995), so these presumed effects have to be tested experimentally.

The *Rfp-Y* region contains a truncated *Y-LB* gene

Part of the *Rfp-Y* region sequence showed homology with a gene encoding a chicken MHC class II β-chain, *B-LBIII* (Zoorob et al. 1990). This gene has since been mapped to the *Rfp-Y* region (Miller et al. 1994b). Figure 6 shows a comparison of the 5′-flanking region, exon 1 and part of intron 1 of the *Y-LB* gene identified in this study with the published full-length *B-LBIII* gene. The promoter elements identified by Zoorob et al. (1990) in the 5′-flanking region of the *B-LBIII* gene (an X/X2 box, an Sp1 binding site and a Y box) are all highly conserved in the promoter of the *Y-LB* gene. Predicted aa identity between the two genes for exon 1 is 83.3%. However, the *Y-LB* gene is truncated, with a stop codon substituted for the R22 in *B-LBIII*. Nucleotide identity between the two genes breaks down in intron 1.

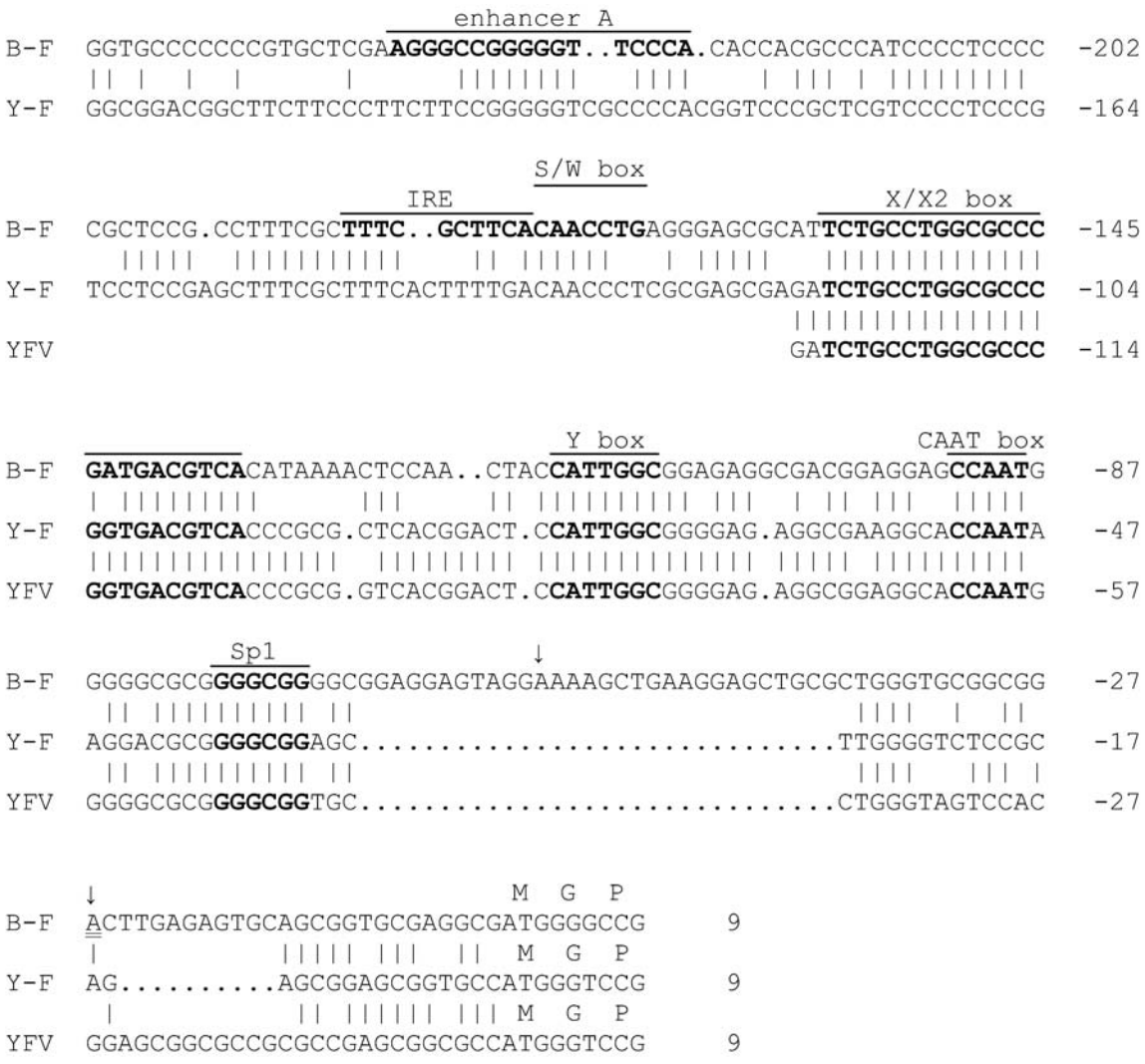


Fig. 5 Comparison of the promoter sequences of *B-F* (Kroemer et al. 1990; van den Elsen et al. 1998), *YFV* (accession no. AF218783, described as the *YFV-Y-FVw*7* allele) and *Y-F* genes. Promoter sequences thought to be involved in expression of the genes are shown *overlined* above the pile-ups and in *bold*. *Vertical lines* indicate nt conserved between *Y-F* and the other genes. Bases are *numbered* with respect to the respective translational start-points. The upstream S/W box in the *Y-F* promoter is not shown. The *arrows* mark the minor (*double underlined*) and major site of transcription initiation of the *B-F* gene, as determined by S1 nuclease mapping (Kroemer et al. 1990)

The *Rfp-Y* region contains a large CR1 element

CR1 elements (Stumph et al. 1981) are a family of non-long-terminal repeat retrotransposons, with approximately 30,000 copies present in the chicken genome (Hache and Deeley 1988; Chen et al. 1991). They have common 3′ ends and variable 5′ truncations, encode a *pol*-like open reading frame (Burch et al. 1993) and have a 4,558-bp consensus sequence (Haas et al. 1997). Approximately 3.3 kb of the *Rfp-Y* region sequence showed homology with CR1 elements.

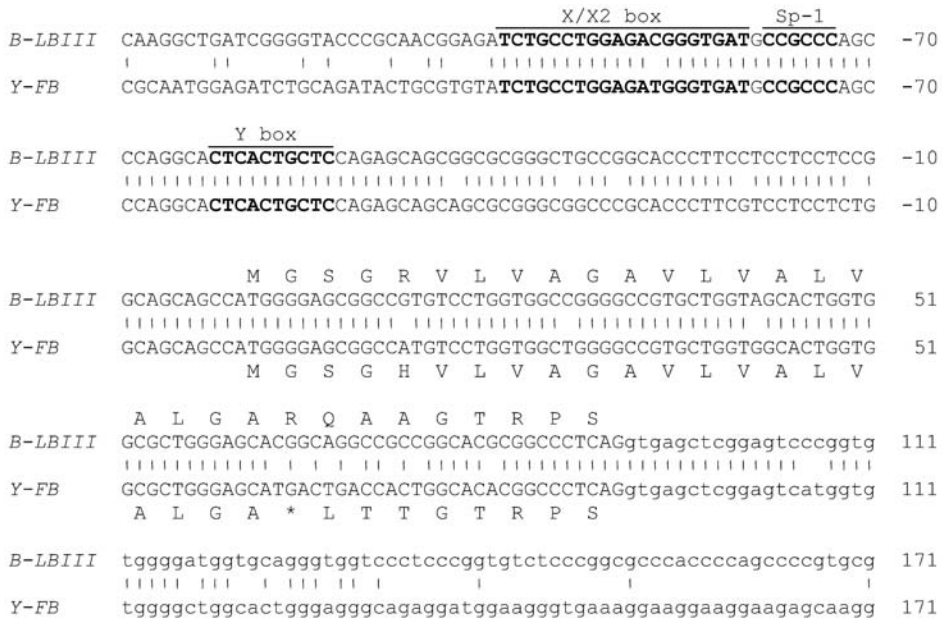


Fig. 6 Comparison of the 5′-flanking region, exon 1 and part of intron 1 of *B-LBIII* and *Y-LB*, showing nt and predicted aa sequences. *Vertical lines* indicate nt conserved between the two genes. Promoter sequences thought to be involved in expression of the two genes are shown *overlined* above the pile-ups and in *bold*. Bases are *numbered* with respect to the respective translational start-points

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