Ef2: A NEW *LY-3*-LINKED LIGHT-CHAIN MARKER EXPRESSED IN NORMAL MOUSE SERUM IMMUNOGLOBULIN*

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Polymorphism associated with mouse immunoglobulin kappa chains has been detected by peptide mapping (1) and isoelectric focusing (IF)[1] of normal serum light chains (2) as well as by IF of the light chains of antiphosphoryl choline antibodies (3). All three markers have been found to share an identical strain distribution; studies involving *Ly-2*^{a}, *3*^{a}-congenic lines (4), as well as the AKXL (5, 6) and NX8 (7) recombinant inbred lines (8) have established that the light-chain markers are closely linked to the *Ly-2* and *Ly-3* loci on Chromosome 6 coding for the lymphocyte differentiation antigens Lyt-2 and Lyt-3 (9, 10). Recent evidence suggesting that the structural gene for C_κ does not reside on Chromosome 6 has led to speculation that the *Ly-3*-linked, light-chain V-region loci may be regulatory rather than structural (11). The possibility that the *Ly-3* locus and light-chain loci may be one and the same locus has also been considered (12).

We report here a new light-chain IF marker (which we propose to call Ef2), showing a strain distribution different from the other light-chain markers and the Ly-3 marker. The finding of the Ef2 marker resulted from the analysis of normal light-chain IF spectra in a large series of the inbred mouse strains. As reported earlier, four light-chain IF-banding patterns are recognizable among the inbred strains (13). Careful analysis of the differences among the four banding patterns, however, indicated that they could readily be explained by postulating the existence of two loci with two alleles at each locus. The first locus, *Igk-Ef1*, has already been described in some detail (6).

Materials and Methods

Mice. NZB/BlNJ mice were purchased as adults from The Jackson Laboratory, Bar Harbor, Maine; C58/J, BALB/cJ, and AKR/J mice were from our own colony and represent the 8–10th inbreeding generation since they were obtained from The Jackson Laboratory in 1976. Serum from all inbred strains listed in Table I was obtained from The Jackson Laboratory. B6.C3 F_1 animals carrying the hypodactyly (*Hd*) mutation were a generous gift of Dr. P. Lane of the Jackson Laboratory.

Isolation of Immunoglobulins. Immunoglobulin was purified from normal mouse serum by absorption onto protein A-Sepharose. For routine light-chain analysis, 0.2 ml of normal mouse serum was used.

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[1] *Abbreviations used in this paper: Hd*, hypodactyly; IF, isoelectric focusing.

Reduction and Alkylation. Reduction and alkylation was carried out using a two-step procedure as described (2). In the initial step, reduction was effected by addition of 25 nmol of DTT followed 30 min later by 50 nmol of [1-^{14}C]iodoacetamide (Amersham Corp., Arlington Heights, Ill. 50 mCi/mmol). In the second step, complete reduction and alkylation was carried out as described (2).

Chain Separation and IF of Light Chains. Heavy and light chains were separated by urea-formate gel electrophoresis as described (6). A guide strip was stained to localize the light-chain zone. The light-chain-containing zone was excised as a strip from the unstained part of the gel and transferred directly to the IF gel at the anode end. The IF gel contained 6.4 M urea and 2% Bio-Lyte (Bio-Rad Laboratories, Richmond, Calif.), pH 3–10. The procedures for IF, fixing, and drying of the gels have been described (6).

Results

Description of the Ef2 Marker. The characteristics of the new marker are illustrated in Fig. 1, which shows the banding patterns of normal light chains of NZB/BlNJ and BALB/cJ mice. The most striking difference between the two patterns is seen as the presence of two discrete bands (63 and 54) in the BALB/c patterns, although several other differences are also evident (e.g., bands 5, 20, and 30). It is interesting to note that the two major bands affected (63 and 54) differ by the characteristic 1-charge spacing (≅0.25 pH U) exhibited by the homologues of typical myeloma light chains. This would suggest that the two bands may actually represent the same subgroup of light chain. In an attempt to characterize more precisely the identity of the band 63/54 light chains, we have screened more than 275 BALB/c myeloma proteins (14) using the IF procedure. We have now identified a total of seven BALB/c myeloma light chains which co-focus with bands 54 and 63 of the normal light-chain pattern. Several of these light chains are illustrated in Figs. 1 and 2. In contrast to the high incidence of band 63/54 light chains among the BALB/c myelomas (7 out of 277), we have not yet identified light chains co-focusing precisely with bands 54 and 63 in a screening of 128 myelomas derived from NZB mice (15). This suggests that the "subgroup" of light chains represented by bands 54 and 63, which is greatly reduced in normal NZB serum Ig, may also be underrepresented in the NZB myelomas. This would be consistent with the suggestion that normal immunoglobulin and myeloma immunoglobulins both represent samplings of sequences from the same V-region repertoire, namely, that expressed in the mature plasma cell compartment (16).

Relationships Between Ef1 and Ef2 Markers. The relationship between the Ef1 and Ef2 markers as they affect the normal light-chain IF profiles is illustrated in Fig. 2. This figure includes examples of two individual mice of each of the four recognized light-chain banding phenotypes.

Close Linkage of the Ef1 and Ef2 Markers. The strain distribution of the Ef2 marker (Table I) indicated that it was distinct from the Ly-2 and Ly-3 markers because strains of the same Ly-2 and Ly-3 type (e.g., NZB/BlNJ and BALB/cJ) (17) differed with respect to the Ef2 marker (Figure 1). Linkage studies (summarized in Table II) have indicated that the locus controlling the Ef2-marker light chains (which we propose to call *Igk-Ef2*) is closely linked to *Ly-3*, because in a total of 95 testcross mice no recombinants have been detected between the Ef2 marker and the *Ly-3*-linked marked Ef1 (Fig. 3).

Linkage of Igk-Ef2 to Hypodactyly (Hd). We have investigated the segregation of the Ef2-light-chain marker with respect to a second Chromosome-6 marker, *Hd* (19). The

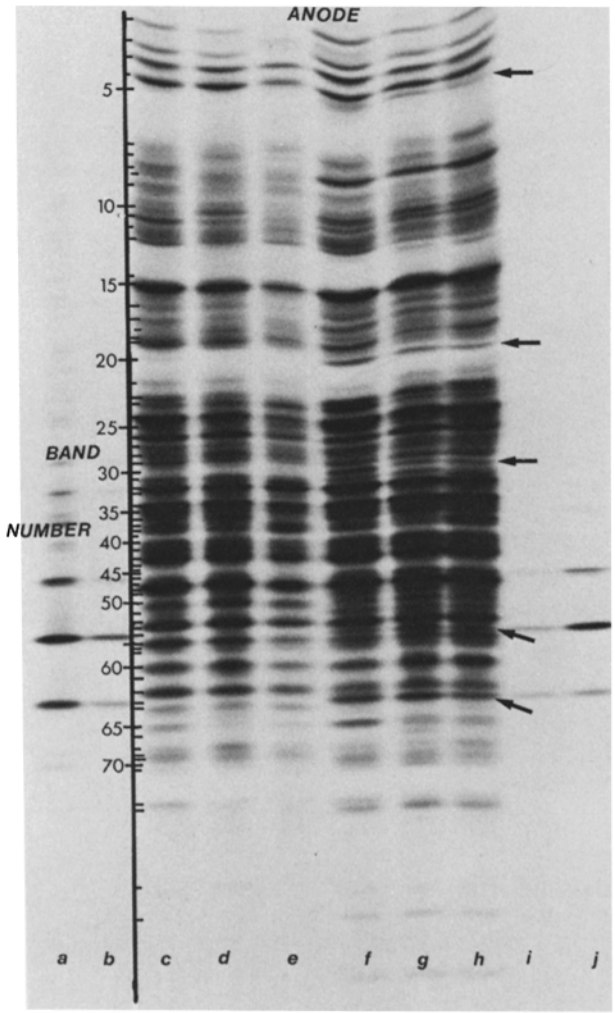

FIG. 1. Light-chain IF patterns illustrating differences controlled by *Igk-Ef2*. Samples (c–e) represent normal light chains of pooled (c) and individual (d, e) NZB/BINJ mice. Samples (f–h) represent normal light chains of individual (f, g) and pooled (h) BALB/c mice. Samples (a), (b), (i), and (j) correspond to light chains of BALB/c myelomas FLOPC-1, FLOPC-21, TEPC (CAL 20)-119, and TEPC-821. These myeloma light chains, as well as the light chains of BALB/c myelomas TEPC (CAL 20)-105, TEPC-817, and TEPC-602, were found to co-focus precisely with the Ef2 marker light-chain bands 63 and 54. Arrows indicate major differences between the *Igk-Ef2*^{a} (BALB/c) and *Igk-Ef2*^{b} (NZB) types. The band numbers are used for reference to the text. In certain instances, improved resolution has revealed additional bands (e.g., 8A) compared to the original numbering scheme (13).

mutation, a semidominant lethal, arose in the inbred strain MYA and was subsequently outcrossed. It is currently maintained by crossing to B6.C3 F_1 hybrid animals. The presence of the *Hd* mutation in the heterozygous state is readily detected as the absence or reduction in the first digit (hallux) of the hind foot. *Hd*/+ animals showed a light-chain banding phenotype identical to that of the parental strains C57BL/6J and C3H/HeJ, indicating that the *Hd* mutation itself did not affect light-chain

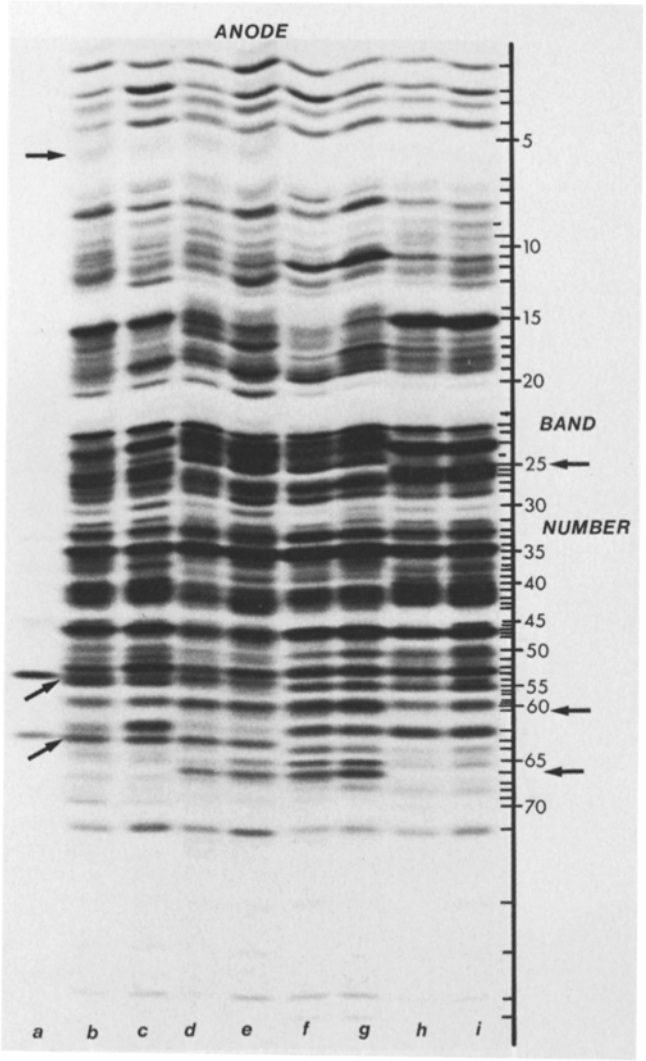

FIG. 2. Normal light-chain IF spectra showing the relationship between the Ef1 and Ef2 markers. Sample (a) represents the light chain of the BALB/c myeloma protein FLOPC-21. Samples (b) and (c) are light chains from two individual BALB/c mice; samples (d) and (e): two individual AKR/J; samples (f) and (g): two individual C58/J; (h) and (i): two individual NZB/BlNJ. Arrows indicate major differences controlled by the *Igk-Ef1* and *Igk-Ef2* loci. The pattern represents a 1-wk autoradiogram of the dried gel.

expression. Because both C57BL/6J and C3H/HeJ mice possess the *Igk-Ef2*^{a}-light-chain allele, linkage of *Igk-Ef2* and *Hd* could be tested by crossing (B6xC58/J)F_1-*Hd*/+ hybrid mice back to C58/J. In 37 out of 37 backcross animals examined we have found complete concordance between the presence of *Hd*- and the Ef2-marker light-chain bands (bands 54/63). This would indicate that the *Igk-Ef2* and *Hd* loci are separated by <9.5 map units (percent recombination) at the 95% confidence limits.

Discussion

We have interpreted differences observed in the IF patterns of normal light chains of inbred mouse strains in terms of a genetic model involving two loci with two alleles

TABLE I

Strain Distribution of Alleles at Igk-Ef1, Igk-Ef2, Ly-2, and Ly-3 Loci *

Strain	*Igk-Ef1*	*Igk-Ef2*	*Ly-2*	*Ly-3*
AKR/J, PL/J, RF/J	a	a	a	a
C58/J	a	b	a	a
A/J, BALB/cJ, BUB/BnJ, C57BL/KsJ, C57BL/6J, C57BL/10J, C57BR/cdJ, C57L/J, CBA/H-T6J, 129/J, LP/J, ST/bJ, SWR/J, SJL/J	b	a	b	b
CBA/J, C3H/HeJ, DBA/1J, DBA/2J, SM/J	b	a	a	b
A/HeJ, A/WySn, A.BY/Sn, CBA/CaJ, C57BL/10Sn, LG/J, RIII/2J	b	a	?	b
BDP/J, CE/J, I/LnJ	b	b	a	b
NZB/BINJ	b	b	b	b
P/J	b	b	?	b

* *Ly-2* and *Ly-3* are summarized from references 10, 18, 6, and 17.

TABLE II

Evidence for Linkage of Igk-Ef1 and Igk-Ef2

	Igk-Ef1						*Igk-Ef2*			
		Band No.						Band No.		
	Allele	25/26	58	60	61	66	Allele	54	63	
Parental, F_1 hybrid strains										
BALB/cJ	b	+	−	+	−	−	a	+	+	
C58/J	a	−	+	−	+	+	b	−	−	
(C58/J × BALB/cJ)F_1	a/b	+	+	+	+	+	a/b	+	+	
NZB/BINJ	b	+	−	+	−	−	b	−	−	
AKR/J	a	−	+	−	+	+	a	+	+	
(AKR/J × NZB/BINJ)F_1	a/b	+	+	+	+	+	a/b	+	+	
Experimental cross I: (C58/J × BALB/cJ)F_1 × NZB/BINJ										Number of animals*
Nonrecombinant	b/b	+	−	+	−	−	a/b	+	+	32
Phenotypes	a/b	+	+	+	+	+	b/b	−	−	28
Recombinant	b/b	+	−	+	−	−	b/b	−	−	0
Phenotypes	a/b	+	+	+	+	+	a/b	+	+	0
Experimental cross II: (AKR/J × NZB/BINJ)F_1 × NZB/BINJ										
Nonrecombinant	a/b	+	+	+	+	+	a/b	+	+	19
Phenotypes	b/b	+	−	+	−	−	b/b	−	−	16
Recombinant	a/b	+	+	+	+	+	b/b	−	−	0
Phenotypes	b/b	+	−	+	−	−	a/b	+	+	0

* No recombinants in 95 instances indicates that the two markers are separated by <3.9 map units (percent recombination) at the 95% confidence limits (chi-square method).

at each locus. The model is attractive because it allows a simple explanation of the four light-chain banding phenotypes so far distinguished. The four phenotypes, as observed in the prototype strains BALB/c, AKR, NZB, and C58, represent the four possible combinations of the two alleles at each locus. The two loci determining the

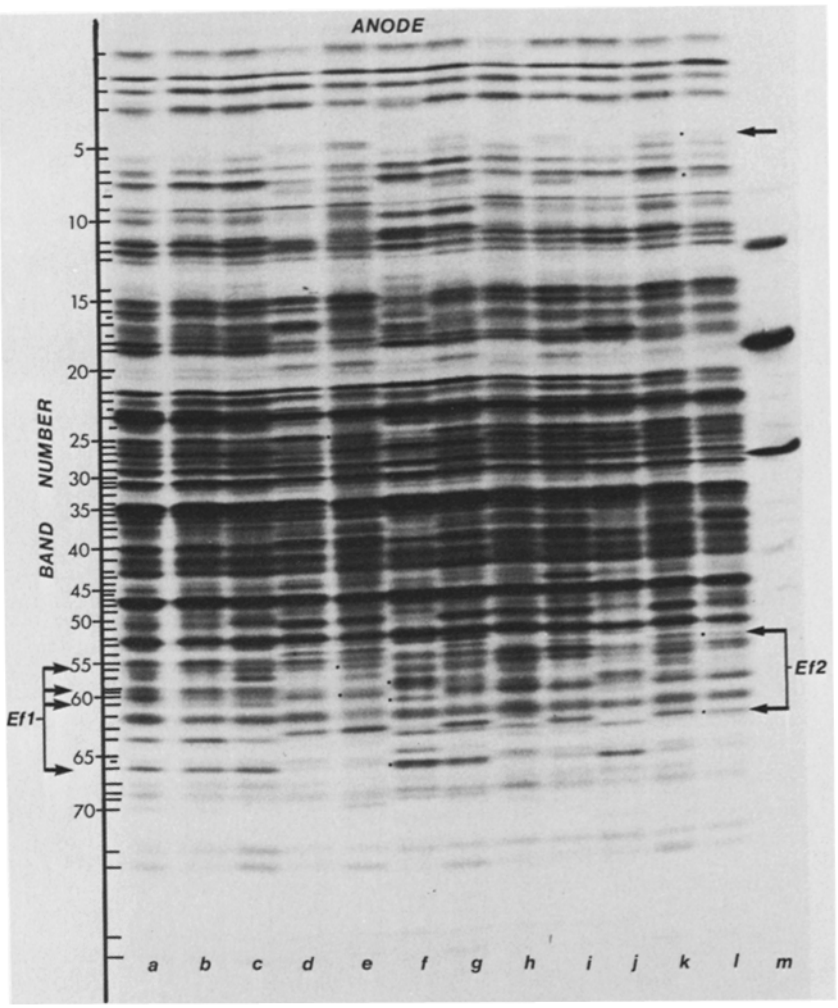

FIG. 3. Normal light-chain IF spectra of parental, F_1 hybrid, and individual testcross mice (experimental cross I, Table II). The parental strains BALB/c J, C58/J, and NZB/BlNJ; and the (BALB/cJ × C58/J)F_1-hybrid patterns are samples (e), (f), (h), and (g), respectively. Samples (a–d) and (i–l) represent light chains from individual testcross animals. Arrows indicate bands controlled by the *Igk-Ef1* and *Igk-Ef2* loci. Band 66 in this gel is not resolved completely from a minor band present in both BALB/c and C58 patterns; it thus appears as an incomplete absence in the testcross patterns. In gels where complete resolution of band 66 is obtained, complete absence is observed in the negative patterns. Clear differences are noted in the case of the better-resolved Ef1-marker bands 58 and 61, and in Ef2-marker bands 63 and 54. Sample (m) represents the light chain obtained from 1 μl of reduced and alkylated ascites fluid from the BALB/c myeloma LPC-1.

banding differences have been designated *Igk-Ef1* and *Igk-Ef2* in accordance with the new guidelines proposed by Green (20). Each of the loci seems to affect the expression of a distinct set of bands in the normal light-chain IF profiles. The differences in several cases appear to involve the complete disappearance of given bands (e.g., Ef1 marker bands 61 and 66 and Ef2 marker bands 54 and 63). In the case of several of the minor bands, however (e.g., Ef2 bands 5, 8, and 20), it is not clear whether the differences observed may be more of a quantitative nature. At least some of the

difficulty in deciding between quantitative and qualitative differences is due to the limitations of resolution. If two components are not completely resolved, the disappearance of one component would not cause the disappearance of an entire band, but only a reduction in its intensity.

Results indicate that *Igk-Ef2* is closely linked to *Igk-Ef1* and hence to *Ly-3* because in a total of 95 testcross mice no recombinants have been found. The Ef2 marker was also found to map close to *Hd*, a second Chromosome-6 marker investigated. Because no recombination has yet been demonstrated between *Igk-Ef1* and *Igk-Ef2*, formal proof of the second locus is lacking. We feel that the alternative explanation of the results, namely, that the patterns are controlled by a single regulatory locus with four alleles, is less satisfactory as the differences are clearly additive in the different phenotypes (e.g., AKR pattern = C58 pattern + bands 54 and 63; and BALB/c pattern = NZB pattern + bands 54 and 63). An additional argument favoring the two-locus model is that in F_1 hybrids of the type (BALB/c × C58)F_1 or (AKR × NZB)F_1, one observes the products of three alleles; bands 66, 61, and 58 ($Ef1^a$); bands 25/26 and 60 ($Ef1^b$); and bands 63 and 54 ($Ef2^a$) (Table II and Fig. 3).

Perhaps the most interesting aspect of the normal light-chain IF markers is that they seem to involve discrete groups of light chains. It is tempting to speculate that the bands observed in the normal light-chain IF profiles correspond to light chains belonging to the same V-region subgroup and, hence, that the differences represent the absence of certain V-region subgroups in some strains of mice. Although this interpretation seems an oversimplification, we have, so far, no evidence that it is incorrect and, indeed, much data support it. A survey of the focusing behavior of BALB/c and NZB light chains of known amino acid sequence indicates that well-defined subgroups of light chains such as λ-1 (21) or V_κ-21 A, B, C, D, E, and F (22, 23) behave precisely according to expectation; i.e., those differing by only neutral substitutions co-focus with each other and correspond to prominent bands present in the normal light-chain IF profiles.[2] In the case of the λ-1 subgroup, for example, all proteins so far examined co-focus with normal light-chain band 22. The supposition that band 22 in the normal pattern actually represents the λ-1 subgroup is supported by the finding that band 22 is greatly reduced in SJL light-chain patterns, consistent with the results of Geckeler et al., (24) who have reported a 50-fold reduction in λ-1 light chains in SJL serum immunoglobulin.

The interpretation of normal light-chain IF bands as representing light chains sharing the same V-region subgroup would lead to the prediction that the BALB/c myeloma light chains corresponding to the Ef2-marker bands (e.g., FLOPC-1, TEPC-817, etc.; Figs. 1 and 2) will define the major subgroup of light chains controlled by the *Igk-Ef2* locus. One would thus expect to find this subgroup greatly reduced or absent in strains bearing the $Igk\text{-}Ef2^b$ allele. Amino acid sequencing of a number of these proteins is currently under way in this laboratory and the results should provide a precise definition of the nature of the Ef2 marker.

In considering candidates for a genetic mechanism operative at the level of the V-region subgroup, one is forced to consider mechanisms operating close to the V-region repertoire itself. Such mechanisms could include differences in the content of V_κ genes or in the factors controlling V_κ-gene expression (e.g., at the level of V-C joining or subsequent processing [25]). Regulatory influences affecting light-chain expression at

[2] Gibson et al. Manuscript in preparation.

the level of clonal proliferation would not be expected to select for given V-region subgroups, because the V-region subgroup itself may be of little functional significance. This follows mainly from the assumption that light chains of a given subgroup may participate in a wide variety of functional combinations with heavy chains of different V_H sequence and C_H class.

We feel that the simplest working hypothesis to explain the present results is still that the differences observed are due to differences in the V_κ-gene repertoire (2). This interpretation has several important implications. Firstly, it suggests that there may be relatively few V_κ-structural genes (e.g., of the order of 100) coding for the bulk of normal serum immunoglobulin light chains, because the discrete differences we observe represent about 1% of the light-chain pattern. This conclusion is not completely out of line with recent estimates based on saturation hybridization that indicate that there may be of the order of 300 V_κ-structural genes in the mouse genome (26). In both instances, a significant role for somatic diversification is implied. A second implication of the structural gene hypothesis is that the genes coding for mouse V_κ sequences must reside on Chromosome 6. The Chromosome-6 location of the V_κ-structural genes, however, is currently a subject of controversy, because conflicting reports have appeared (11, 27). Interpretation of the results as due to differences in V_κ-structural genes also has implications for the recently proposed gene rearrangement model (23). In this model, each V_κ gene (coding for amino acid positions 1–98) (28) may integrate with any one of several J segments (coding for amino acid positions 99–112) (29). Each V_κ gene would thus give rise to a set of gene products representing the V sequence in combination with different J segments. Examination of the available sequence data indicates that the majority of amino acid sequence differences in the J segment are neutral in character and would therefore not affect the IF position of the light chain. At least one J sequence (e.g., that associated with the NZB light chain 2413), does differ by charge, however, and this would be expected to shift the position of the light chain anodally by 4 charge U (23). It is interesting to note that although the major difference determined by *Igk-Ef2* involves bands 63 and 54, other linked differences (e.g., bands 20, 30, etc.) are observed $\cong$ 3 and 4 charge U anodal to the major difference. Close analysis of the differences, has indicated that the spacing between bands 63 and 54, and the more anodal pair, 30 and 20, is too large to be explained by precise 3 and 4 charge U differences. We therefore feel it is unlikely that the differences in the region of band 30 can be simply explained as due to band 63 light chains with a more acidic J segment. Further analysis of the linked differences controlled by the *Igk-Ef1* and *Igk-Ef2* loci, however, may well be informative for establishing the extent to which J-region differences affect the normal light-chain IF patterns.

Interpretation of the present results is also possible by postulating an *Ly-3*-linked regulatory locus, or by supposing that the *Ly-3* locus itself governs the expression of light chains, but the regulatory interpretation becomes more unwieldy with the demonstration of additional V-region loci.

Summary

A new light-chain marker has been detected in normal mouse serum immunoglobulin light chains by gel isoelectric focusing. The marker (Ef2) involves the presence of two major and several minor bands in the normal light-chain IF profiles. Strains

expressing the marker IF bands are designated *Igk-Ef2*^{a}, whereas those lacking the bands are *Igk-Ef2*^{b}. The majority of inbred strains are *Igk-Ef2*^{a}. Strains found to be *Igk-Ef2*^{b} are NZB/BlNJ, BDP/J, C58/J, I/LnJ, CE/J, and P/J. The strain distribution of the alleles differs from the distribution of alleles at the *Ly-2* and *Ly-3* loci, suggesting the new marker may represent a separate locus. Genetic studies have shown that *Igk-Ef2* locus is closely linked to *Igk-Ef1* and *Hd* loci on Chromosome 6, indicating that it is also closely linked to *Ly-3*. The relative importance of the bands controlled by the *Igk-Ef2* locus suggests that the entire normal light-chain pool could be controlled by as few as 100 such loci.

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