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Structural and Functional Properties of Human λ-Light-Chain Variable-Region Subgroups

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INTRODUCTION

The two types of human light chains, κ and λ, are found among all classes of immunoglobulin (Ig) molecules and are characterized by a common structure consisting of ~107 amino-terminal amino acid residues, which is the variable (V) region, and ~107 carboxyl-terminal residues, which is the constant (C) region. The light-chain V region (V_L) is specified by two gene segments, V and J, that encode the first 95 to 98 amino acids and the following 12 (κ) or 13 (λ) joining (J)-region residues, respectively. The light-chain C region (C_L) is encoded by a third gene, C. Despite their structural similarity, κ and λ light chains are the products of genes that differ profoundly in location, number, and organization. The human κ-light-chain locus, found on chromosome 2, contains multiple V_κ genes, five tandemly arranged J-gene segments, and one C_κ gene. The human λ-light-chain locus, situated on chromosome 22, also contains multiple V_λ genes but differs from κ in the number of C_λ genes (at least seven, of which four are functional) and by the association of each with a particular J_λ-encoding segment. Notably, λ-light-chain-gene recombination occurs only after failure of either κ allele to rearrange productively. The extensive diversity in human light-chain V-region sequences reflects primarily the number of functional V_κ or V_λ genes (~40 each), as well as substitutions caused by somatic mutation. Additional diversity results from the combinatorial joining of V- and J-gene segments and the variation introduced at the site of V-J recombination, including the insertion of extra bases (P or N nucleotides).

The elucidation of human light-chain-related genes and their regulatory factors is fundamentally important to understanding B-cell development as well as antibody structure and function. Especially relevant is the pathogenic relationship between light-chain-gene expression and neoplastic and autoimmune disease. Compared with κ, considerably less information is available on λ, particularly in regard to the structural features of V_λ genes. However, λ light chains are biologically important, as evidenced by the fact that they are found on ~30 to 40% of human Ig molecules in the normal state and to an even greater extent in individuals with certain malignant and inflammatory disorders. The purpose of this minireview is to summarize the existing knowledge on the human V_λ locus and to elucidate the biologic, chemical, and functional properties of its protein products as well as their clinical relevance.

HUMAN V_λ GENES

Sequence and immunochemical analyses of Bence Jones proteins and light chains isolated from monoclonal Igs have provided considerable insight into the structural diversity of human light chains. Notably, the V_L contains three regions of extensive sequence variability termed the hypervariable or complementarity-determining regions (CDRs); these areas are involved in the antigen-binding and idiotype sites. The remaining portions of the V_L consist of four regions of lesser sequence variability that provide a structural framework for the CDRs and are thus designated the framework regions (FRs). Homologies in sequence, especially in FR1, initially provided the chemical basis for classification of λ (and κ) light chains into multiple subgroups (28). These V_L subgroups are isotypic in nature; i.e., molecules representative of each are found among Ig light chains in normal serum (2). Five of the six V_λ subgroups ($V_{\lambda I}$, $V_{\lambda II}$, $V_{\lambda III}$, $V_{\lambda IV}$, and $V_{\lambda VI}$) were recognized by polyclonal and monoclonal anti-light-chain reagents (1, 40). However, in the case of the sixth subgroup, $V_{\lambda V}$, those proteins originally designated as members of this subgroup reacted exclusively with anti-$V_{\lambda II}$-specific reagents and were thus reclassified as λII (1, 40). Subsequently, at the molecular level, the genes encoding the five V_λ subgroups were identified (3, 4, 7, 9, 12, 14–17, 22–24, 27, 38, 46, 49, 51), and Southern blotting data confirmed that the $V_{\lambda V}$ and $V_{\lambda II}$ subgroups were indistinguishable (15).

Through isolation and amplification of cDNA libraries derived from monoclonal B-cell populations of RNA and cloning and sequencing of genomic DNA with subgroup-specific primers, seven additional V_λ-gene families have since been recognized. They were termed $V_{\lambda VII}$ (5, 14), $V_{\lambda VIII}$ (11, 18, 36, 42), $V_{\lambda IX}$ (18, 49), $V_{\lambda X}$ (43), T1 (6), V_λN.2 (15), and Vλ8/DPL21 (49, 50). Furthermore, the multigene nature of certain V_λ-gene families (particularly $V_{\lambda I}$, $V_{\lambda II}$, and $V_{\lambda III}$) has been evidenced by Southern blotting under conditions of high stringency. These V_λ subgroups have been divided into sub-subgroups on the basis of sequence and/or serologic similarities (14–17, 19, 21, 22, 24, 27, 40, 44, 49).

Thus, among the ~70 genes that make up the human V_λ locus (5) (of which about one-half are potentially functional [17, 49]), it is probable that virtually all of the V_λ-gene families have been identified. Although the criteria as to what constitutes a distinct family or subgroup have not been firmly established, traditionally, this differentiation has been made on the basis of a >90 or >80% sequence homology at the nucleotide or protein level, respectively. Sub-subgroups display an even higher degree of identity among family members.

The prototypic nucleotide and translated protein sequences of the functional human V_λ germline genes encoding the 12 presently characterized V_λ subgroups (and sub-subgroups) are given in Fig. 1.

V_λ-gene-family nomenclature. As stated above, the classification of V_λ genes and their expressed products into distinct subgroups or families (designated by Roman numerals) has been based on sequence homologies and serologic analyses.

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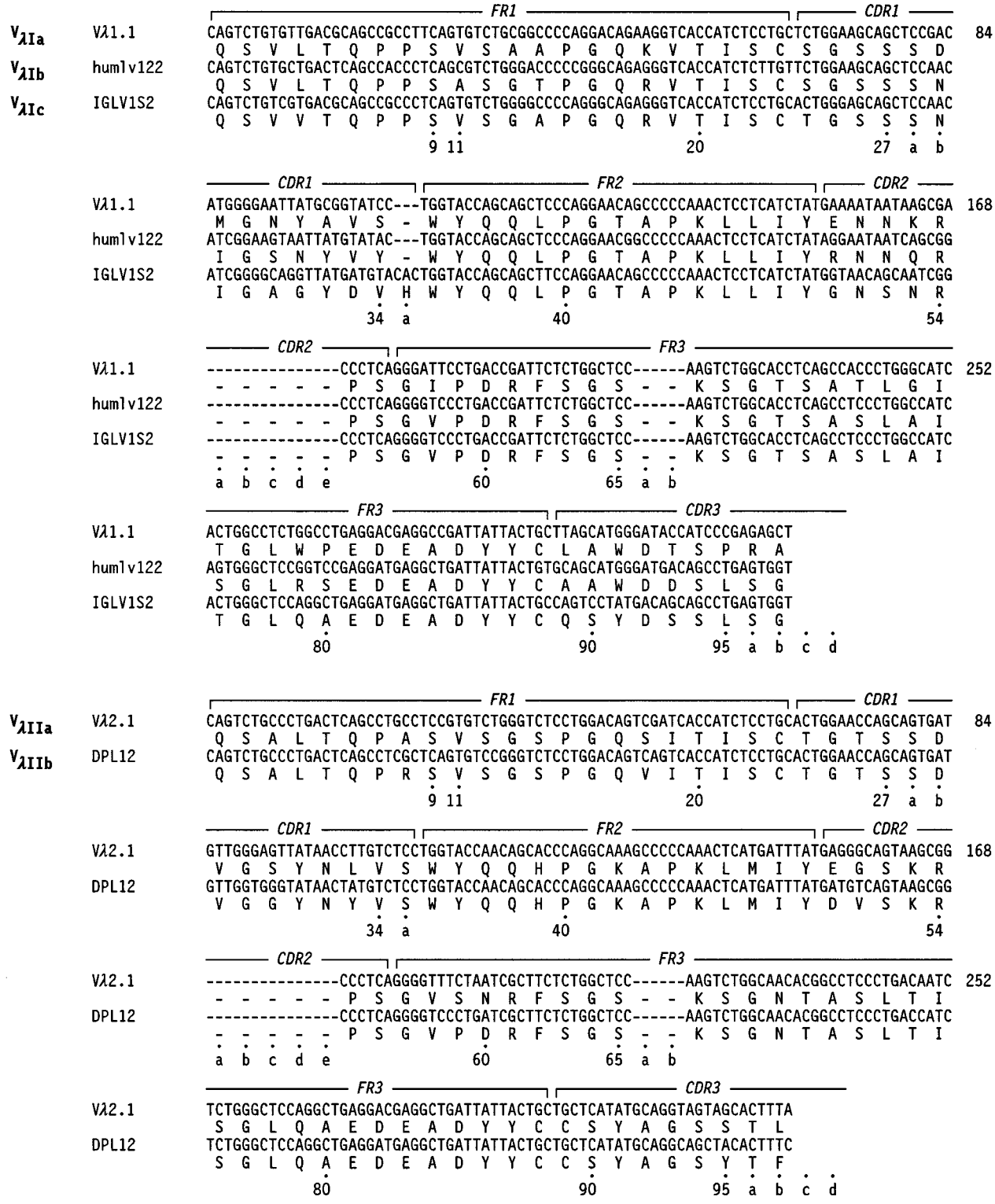

FIG. 1. Nucleotide and deduced amino acid sequences of prototypic germline genes encoding human V_λ subgroups and sub-subgroups. The numbering system used is that of Kabat et al. (28). The presence of additional FR and CDR residues is indicated by lowercase letters.

Unfortunately, considerable confusion concerning nomenclature has been generated because of misclassification (23, 28, 29), arbitrary reassignment of newly recognized V_λ subgroups into previously defined categories (14), and use of previously termed V_λ subgroup numbers for completely different V_λ-gene families (14, 50). A summary of published V_λ-subgroup or -gene-family designations, as well as our proposed nomenclature system, is given in Table 1. A listing of the $V_{\lambda I}$, $V_{\lambda II}$, and

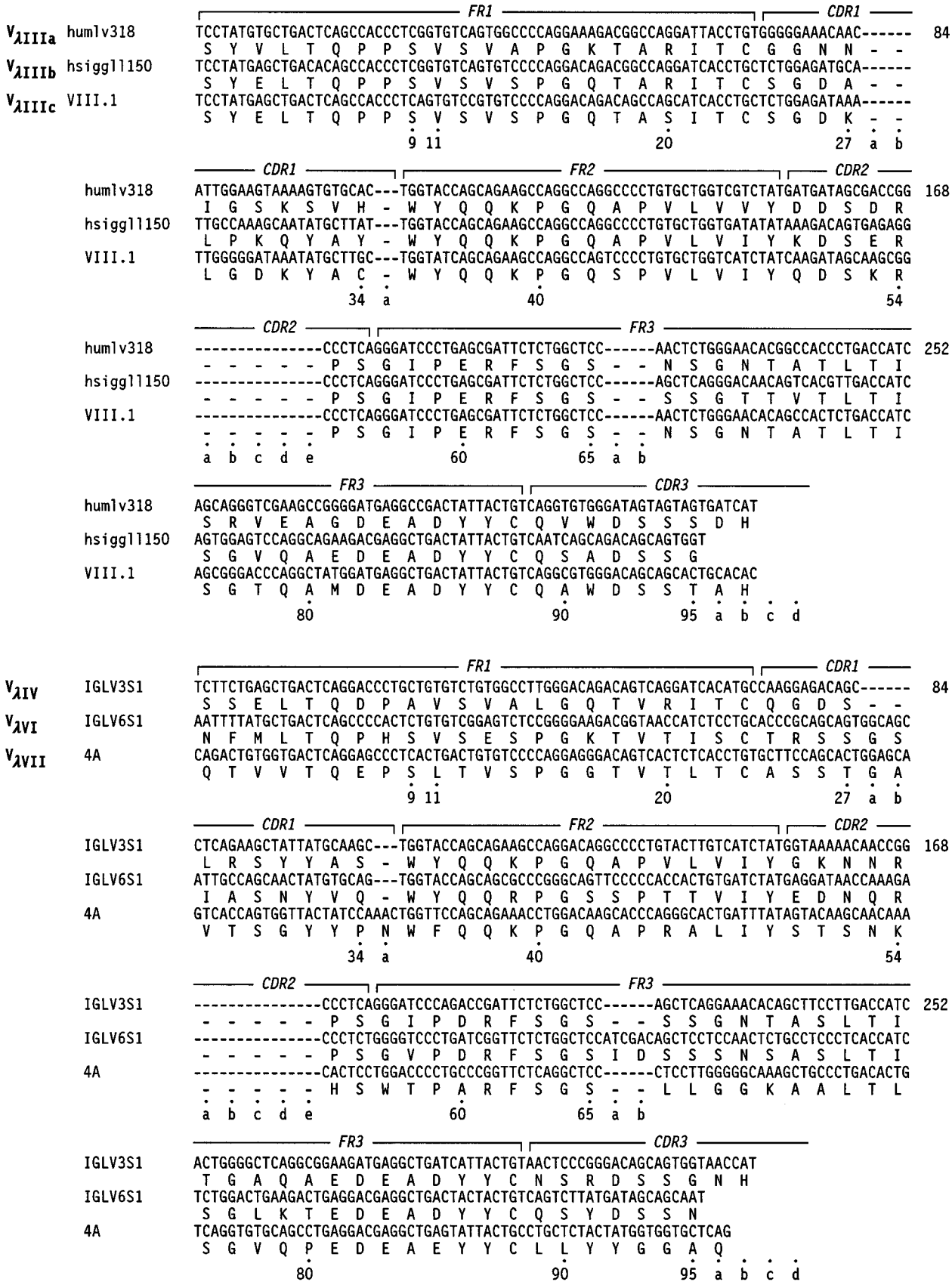

FIG. 1—*Continued.*

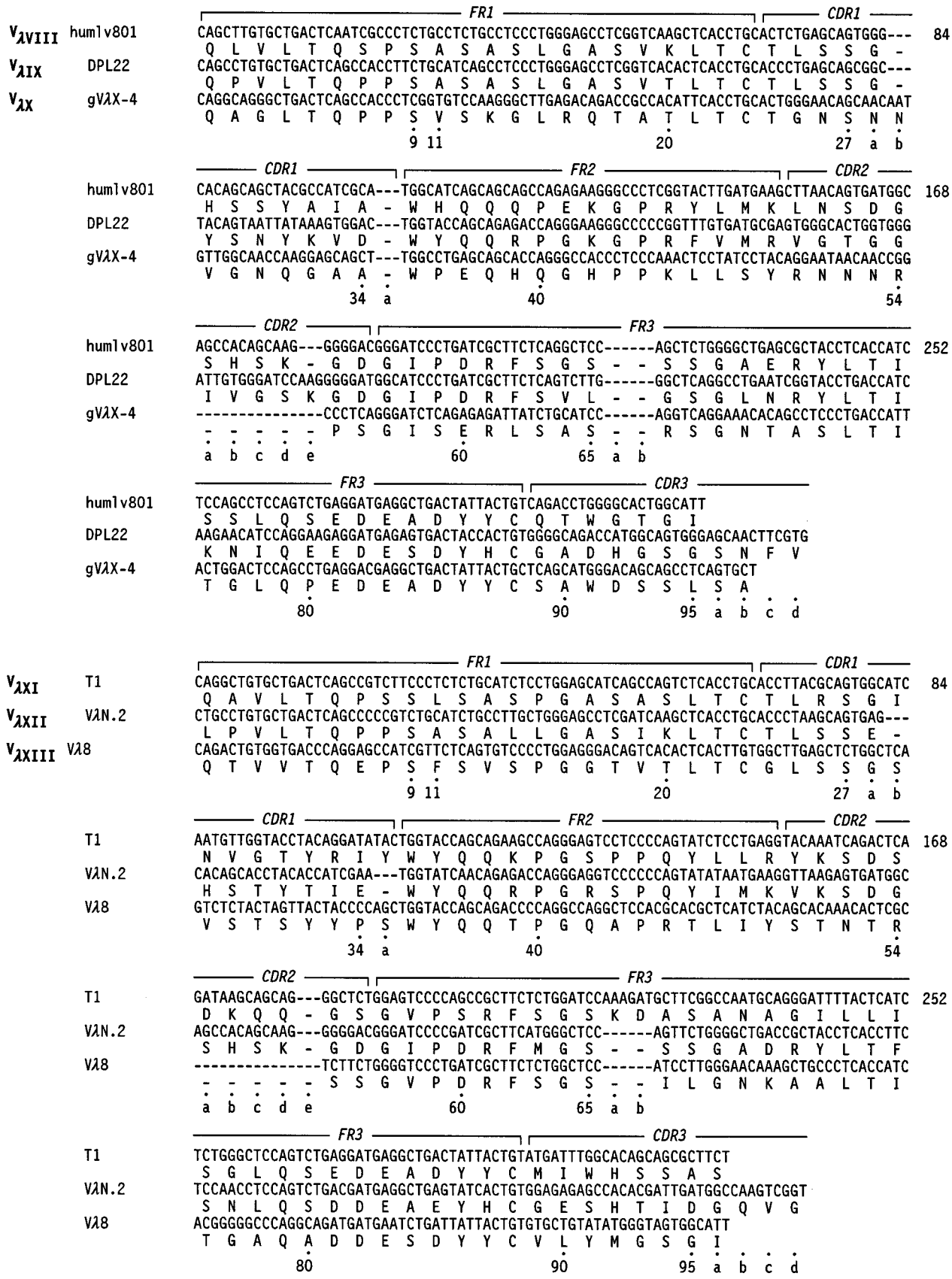

FIG. 1—*Continued.*

TABLE 1. Designation of human V_λ subgroups or gene families

Subgroup or gene family				
Kabat et al. (29)[a]	Chuchana et al. (14)[a]	Combriato and Klobeck (15)[a]	Solomon and Weiss (40)[b]	Recommended
$V_{\lambda I}$	$V_{\lambda I}$	$V_{\lambda I}$	$V_{\lambda I}$	$V_{\lambda I}$
$V_{\lambda II}$[c]	$V_{\lambda II}$	$V_{\lambda II}$	$V_{\lambda II}$	$V_{\lambda II}$
$V_{\lambda III}$	$V_{\lambda III}$[d]	$V_{\lambda III}$	$V_{\lambda III}$	$V_{\lambda III}$
$V_{\lambda IV}$	New $V_{\lambda IV}$ (PK)	$V_{\lambda IV}$	$V_{\lambda IV}$	$V_{\lambda IV}$
$V_{\lambda V}$	New V_V (T1)	($V_{\lambda II}$)[e]	($V_{\lambda II}$)[e]	—[f]
$V_{\lambda VI}$	$V_{\lambda VI}$	N1 ($V_{\lambda VI}$)	$V_{\lambda VI}$	$V_{\lambda VI}$
—	$V_{\lambda VII}$	N2 (V4A)	—	$V_{\lambda VII}$ (4A)
—	—	N4 (VPK)	$V_{\lambda VIII}$ (PK)	$V_{\lambda VIII}$ (PK)
—	—	—	—	$V_{\lambda IX}$ (DPL22)
—	—	—	—	$V_{\lambda X}$
—	—	N3 (VT1)	—	$V_{\lambda XI}$ (T1)
—	—	—	—	$V_{\lambda XII}$ (V_λN.2)
—	—	—	—	$V_{\lambda XIII}$ (Vλ8/DPL21)

[a] Classification based on perceived protein and/or nucleotide sequence homologies.
[b] Classification based on serologic differentiation with polyclonal (40) and monoclonal (2) reagents.
[c] Included within the $V_{\lambda II}$ subgroup were λVII (5) and λVIII (31) proteins.
[d] Included within the $V_{\lambda III}$ subgroup were chemically (28, 29) and serologically (2, 40) defined λIV proteins.
[e] The $V_{\lambda V}$ and $V_{\lambda II}$ subgroups were considered synonymous.
[f] —, $V_{\lambda V}$ designation omitted.

$V_{\lambda III}$ sub-subgroups and their corresponding germline genes are provided in Table 2. For purposes of consistency in naming V_λ subgroups, we recommend that any *newly* recognized V_λ-gene families or sub-subgroups be indicated by consecutive Roman numerals or letters, respectively, on the basis of the order of discovery as determined by publication date. Final terminology will ultimately depend on elucidation of the entire human V_λ locus.

Organization of human V_λ genes. In contrast to the extensive molecular characterization of the human V_κ locus (for a review, see reference 52), similar information on V_λ has only recently become available. Studies to date indicate that $V_{\lambda VI}$, $V_{\lambda X}$, and $V_{\lambda I}$ genes are most distant from the J_λ-C_λ complexes, while $V_{\lambda III}$ and $V_{\lambda II}$ are closest in proximity (15, 24, 43). The positions of these gene families along the chromosome and that of the $J_\lambda C_\lambda$ segments are schematically indicated in Fig. 2. It should be noted that (as for V_κ) these V_λ-gene families are not necessarily segregated but can be interspersed; e.g., while the majority of $V_{\lambda I}$ and $V_{\lambda II}$ genes have been mapped to the 5′ and 3′ portions of the V_λ locus, respectively, members of both gene families have been identified in opposite locations.

Although sequence variations have been noted in the V_λ-associated promoter, TATA box, and leader exons (12, 24, 43, 46, 49), subgroup-related differences have not as yet been found. All V_λ exons have an identical nonamer and heptamer recombination signal sequence and can combine with any of the four functional J_λ genes (43, 45). Furthermore, as in the case of κ genes, V_λ-J_λ recombination results from a deletion mechanism (15, 24).

Structural characteristics of human V_λ subgroups. The human V_λ subgroups are distinguished not only by amino acid sequence homologies but also by the presence of characteristic numbers of residues within CDRs as well as FRs. As indicated in Table 3, these differences are most evident in CDR1 (11 to 14 residues), CDR2 (7 to 12 residues), and CDR3 (7 to 11 residues). The number of CDR3 residues reflects not only V_λ exon nucleotide composition but also the variation resulting from V-J recombinational events and the introduction of P or N nucleotides (30, 47). In FR1, certain λIII light chains contain 21, rather than 22, residues, and λVI and λXI (T1) components are characterized by two additional FR3 residues. Although data on the tertiary structural features of λ light chains are limited, it would be expected that the compositional differences found among the V_λ subgroups, particularly those in the CDRs, would significantly affect the nature of the antigen-binding site (13).

Expression of human V_λ genes in normal and disease states. The light-chain products of the >40 functional human V_λ genes identified to date have been found among monoclonal serum and urinary λ-type Igs and/or $sIg\lambda^+$ B-cell populations. That these V_λ-gene products are expressed in the normal state has been evidenced through serologic analyses of serum and lymphocytes taken from healthy individuals. We have used our monoclonal antibodies specific for λI, λII, λIII (λIIIa, λIIIb,

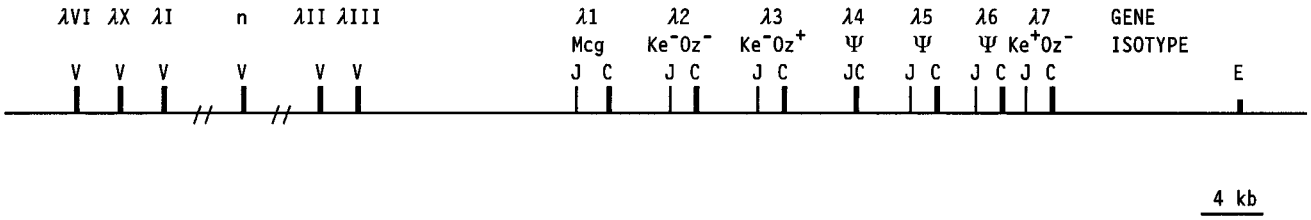

FIG. 2. Characterization of the human λ-light-chain locus. The relative positions of the V_λ- and $J_\lambda C_\lambda$-gene families are based on data given previously (15, 24, 43, 45). Distance within the V region is not to scale; the 3′ λ enhancer (E) is 11.7 kb 3′ of $C_\lambda 7$ (the figure was modified from reference 8). n, tentative location of other human V_λ-gene families.

TABLE 2. Nomenclature and germline equivalents of V_λ subsubgroups

Subgroup and sub-subgroup	Germline genes	Reference
$V_{\lambda I}$		
a	Vλ1.1[a]	3
	humlv117[a]	38
	humlv119, humlv1041	16
	DPL1, DPL4	49
b	humlv1L1, humlv122	16
	DPL2, DPL3, DPL5	49
c	IGLV1S2	7
	humlv101, humlv1042	16
	DPL6, DPL7, DPL8, DPL9	49
$V_{\lambda II}$		
a	Vλ2.1	9
	hslv2066, hslv215.23	27
	DPL10, DPL11	49
b	hslv2007, hslv2031, hslv2046, hslv2011, hslv2113, hslv2132, hslv216.21	27
	DPL12, DPL13	49
$V_{\lambda III}$		
a	humlv318	17
	IGLV3S2	24
b	hsiggll150, hsiggll295	22
c	VIII.1[b]	15

[a] Vλ1.1 and humlv117 were assigned to the $V_{\lambda Ib}$ sub-subgroup by Combriato and Klobeck (15).
[b] Designated λIIId by Frippiat and LeFranc (24).

λIIIc), λIV, λVI, and λVIII light chains (1, 2, 34) to determine the concentrations and relative distributions of these particular subgroups and sub-subgroups among polyclonal λ-type Ig molecules contained in the serum of healthy adults (Table 4). Summation of the relative concentration of each of these six V_λ subgroups was comparable to that of total λ chains as determined with an anti-C_λ reagent. This finding would indicate that the λIX, λX, λXI (T1), λXII (V_λN.2), and λXIII (Vλ8/DPL21) subgroups (for which there are as yet no available antibodies) represent <1% of the total λ-light-chain population. Additionally, the V_λ-subgroup distribution among $sIg\lambda^+$ B-cell populations in healthy adults was comparable to that of polyclonal serum λ-type Igs (42a).

TABLE 3. Number of residues comprising FRs and CDRs of human V_λ subgroups

Subgroup	No. of residues					
	FR1[a]	CDR1	FR2	CDR2	FR3	CDR3
$V_{\lambda Ia}$	22	13	15	7	32	9
$V_{\lambda Ib}$	22	13	15	7	32	9
$V_{\lambda Ic}$	22	14	15	7	32	9
$V_{\lambda IIa}$	22	14	15	7	32	9
$V_{\lambda IIb}$	22	14	15	7	32	9
$V_{\lambda IIIa}$	22	11	15	7	32	9
$V_{\lambda IIIb}$	22	11	15	7	32	7
$V_{\lambda IIIc}$	22	11	15	7	32	9
$V_{\lambda IV}$	22	11	15	7	32	9
$V_{\lambda VI}$	22	13	15	7	34	7
$V_{\lambda VII}$	22	14	15	7	32	8
$V_{\lambda VIII}$	22	12	15	11	32	7
$V_{\lambda IX}$	22	12	15	12	32	11
$V_{\lambda X}$	22	13	15	7	32	9
$V_{\lambda XI}$	22	14	15	11	34	7
$V_{\lambda XII}$	22	12	15	11	32	11
$V_{\lambda XIII}$	22	14	15	7	32	8

[a] FR1 of certain expressed λIIIa, λIIIb, λIIIc, and λIV light chains contains 21 residues (20, 21).

TABLE 4. V_λ-subgroup distribution among λ-type Igs in normal serum[a]

Subgroup	Mean concn ± SD (μg/ml)	Relative %
$V_{\lambda I}$	1,775 ± 404	39.9
$V_{\lambda II}$	134 ± 36	3.0
$V_{\lambda III}$	1,917 ± 725	43.1
$V_{\lambda IV}$	241 ± 50	5.4
$V_{\lambda VI}$	238 ± 97	5.4
$V_{\lambda VIII}$	140 ± 51	3.2
Total λ	4,445 ± 821	100.0

[a] Data are from reference 34.

In contrast to the healthy state, in which IgλI, IgλII, IgλIII, IgλIV, IgλVI, and IgλVIII molecules represent ~40, 3, 43, 5, 5, and 3%, respectively, of the total Igλ population, certain V_λ-gene families are preferentially expressed in individuals with monoclonal plasma cell- and B-cell-related neoplastic or immunoproliferative disorders (34) (Table 5). Serologic analyses of λ-type IgG, IgA, and IgD myeloma proteins and Bence Jones proteins obtained from 196 patients with multiple myeloma and related gammopathies and 41 patients with light-chain-associated (AL) amyloidosis revealed approximately nine- and sevenfold higher percentages of λII components, respectively; among 16 Waldenström's macroglobulins, two-thirds were classified as IgMλII. The functional importance of this V_λ subgroup has been evidenced by its association with certain autoimmune and antibacterial antibodies; e.g., the $V_{\lambda II}$-gene family encodes exclusively for the λ-light-chain-related 8.12 idiotype present on one-third of anti-DNA antibodies found in the sera of patients with systemic lupus erythematosus (35).

Our analyses of associated Igs confirmed that the $V_{\lambda VI}$ subgroup is preferentially associated with this form of amyloidosis (39); 17 of 41 amyloid-associated proteins were classified as IgλVI. To date, we have found no $V_{\lambda VI}$-related components among λ-type myeloma proteins, Waldenström's macroglobulins, IgM rheumatoid factors, or $sIg\lambda^+$ chronic lymphocytic leukemia cell populations (34, 41).

TABLE 5. V_λ-subgroup distribution among λ-type polyclonal and monoclonal Igs

Subgroup	% Distribution				
	Normal[a]	MM[b]	AL[b]	WM[b]	RF[c]
$V_{\lambda I}$	40	27	10	22	11
$V_{\lambda II}$	3	28	20	64	7
$V_{\lambda III}$	43	39	29	7	44
$V_{\lambda IV}$	5	5	0	7	19
$V_{\lambda VI}$	5	0	41	0	0
$V_{\lambda VIII}$	3	1	0	0	19

[a] Polyclonal Igλ in serum from 20 healthy adults.
[b] Monoclonal IgG, IgA, IgD, and Bence Jones proteins obtained from 196 patients with multiple myeloma (MM), 41 with light-chain-associated amyloidosis (AL), and 16 with Waldenström's macroglobulinemia (WM). Data are from reference 34.
[c] Monoclonal IgMλ rheumatoid factors (RFs) produced by 27 immortalized peripheral blood or synovial B cells from patients with rheumatoid arthritis (11, 20, 34a).

Other examples of the skewed distribution of V_λ subgroups include monoclonal IgMλ rheumatoid factors produced by Epstein-Barr virus-immortalized cell lines prepared from peripheral blood or synovial B cells from patients with rheumatoid arthritis (22, 36) (Table 5). In these cases, we have found that the percentages of the relatively uncommon $V_{\lambda IV}$ and $V_{\lambda VIII}$ subgroups were increased approximately four- and sixfold, respectively, above normal (20, 42). Additionally, a predominance of λIIIb-containing proteins was evidenced among IgMλ rheumatoid factors having specificity for rabbit IgG (19, 22). An apparently biased expression of the $V_{\lambda IV}$ subgroup with other types of autoantibodies has also been demonstrated, e.g., among anti-D(Rh) (10), antilysozyme (33), antithyroglobulin (26), and antisperm antibodies (51), as well as in $sIg\lambda^+$ chronic lymphocytic leukemia cell populations (41). The λVII nature of vaccine-induced anti-*Haemophilus influenzae* type b polysaccharide antibodies bearing the cross-reactive idiotype HibId-2 (25) and the association of λIX and λXIII (Vλ8/DPL21) light chains with other types of autoantibodies have also been reported (32, 49, 50). Additionally, a preferential usage of λI light chains was noted among anti-gp120 antibodies in the sera of human immunodeficiency virus type 1-infected individuals (48).

The molecular basis for the nonstochastic expression of V_λ subgroups in patients with neoplastic and inflammatory diseases is unknown. Whether the use of specific V_λ-gene families in these disorders reflects (i) the propensity of particular B cells to undergo Epstein-Barr virus-induced transformation, (ii) a unique antibody response, (iii) chromosomal location (i.e., the proximity to $J_\lambda C_\lambda$ segments), or (iv) alterations in transcriptional regulation remains to be established. Alternatively, the apparent overexpression of particular V_λ genes may be related to their possible overrepresentation in the fetal repertoire, as has been found for certain V_H-gene families (37).

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