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Genetics

Human immunoglobulin $C_\lambda 6$ gene encodes the Kern$^+$Oz$^-$ λ chain and $C_\lambda 4$ and $C_\lambda 5$ are pseudogenes

(isotypes/allotypes/Bence Jones proteins/constant region genes)

P. DARIAVACH, G. LEFRANC, AND M.-P. LEFRANC

Laboratoire d'Immunogénétique, Centre National de la Recherche Scientifique Unité Associée 1191, Génétique Moléculaire, Université des Sciences et Techniques du Languedoc, Place E. Bataillon, 34060 Montpellier Cedex, France

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ABSTRACT **Six nonallelic immunoglobulin λ constant region genes have been previously characterized on a 40-kilobase stretch of DNA. The nucleotide sequences of the three upstream genes of this cluster ($C_\lambda 1$, $C_\lambda 2$, $C_\lambda 3$) have been determined by other workers and shown to encode, respectively, the isotypic Mcg, Kern$^-$Oz$^-$, and Kern$^-$Oz$^+$ constant region of the λ chains. In this paper, we report the sequence of the three downstream genes of this cluster and show that two of them ($C_\lambda 4$ and $C_\lambda 5$) are pseudogenes. However, $C_\lambda 6$ encodes a Kern$^+$Oz$^-$ chain and corresponds to the fourth isotype described among the λ proteins sequenced so far. A potentially active J_λ (joining) segment, with the canonical heptamer and nonamer sequences for rearrangement, is located 1.5 kilobases upstream of $C_\lambda 6$. The amino acid sequence encoded by the $C_\lambda 6$ gene is compared with the constant region sequences of various monoclonal Bence Jones λ proteins. Allotypic and isotypic differences confirm the polymorphism and complexity of the human C_λ locus.**

In humans, the constant (C) region of the immunoglobulin λ light chains consists of at least four nonallelic or isotypic forms that differ by limited amino acid substitutions to produce the serological markers Kern (Ke) (1, 2), Oz (3–5), and Mcg (6, 7). Several additional substitutions have been described (8–16), but it is unknown whether these represent allelic variants or distinct isotypes. The human immunoglobulin λ light chain genes have been mapped to chromosome 22 (17) at band q11 (18, 19), and six nonallelic λ C region genes ($C_\lambda 1$ to $C_\lambda 6$) have been characterized on a 40-kilobase (kb) stretch of DNA (20). The number of C_λ genes varies between six and nine per haploid genome (21). These variations were detected by restriction fragment length polymorphism (21) and seem to have arisen from unequal meiotic crossing-over with a duplication of the $C_\lambda 2$ and $C_\lambda 3$ genes. Moreover, three additional C_λ-like genes have been recently identified, which map on different stretches of DNA and are nonallelic (22). One of these is a pseudogene, whereas the two others encode a putative λ chain C region whose sequence differs from that of the λ chains described so far.

Only three C_λ genes ($C_\lambda 1$, $C_\lambda 2$, and $C_\lambda 3$) belonging to the cluster described by Hieter have been sequenced (20), and they have been shown to encode, respectively, the Mcg, Ke$^-$Oz$^-$, and Ke$^-$Oz$^+$ C region of the λ chains. In this paper, we report the sequences* of the three genes located downstream in this cluster and show that two of them ($C_\lambda 4$ and $C_\lambda 5$) are pseudogenes, whereas $C_\lambda 6$ encodes a Ke$^+$Oz$^-$ chain, the fourth isotype described among the proteins sequenced so far. This $C_\lambda 6$ gene has a potentially active $J_\lambda 6$ joining region, with the canonical heptamer and nonamer sequences for rearrangement, 1.5 kb upstream of the coding C region.

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MATERIALS AND METHODS

Construction of a Phage Library from LY67 DNA. DNA prepared from LY67 cells (a λ-producing Burkitt's lymphoma) (23) was partially digested with *Mbo* I. Restriction fragments 15–20 kb long were ligated into *Bam*HI-digested DNA of phage λ2001 (24) and packaged *in vitro*. Recombinant phages were screened by the *in situ* plaque hybridization procedure (25).

Probes. A genomic clone (Chr 22λ5) in λgt-λWES (26) was kindly provided by T. H. Rabbitts (Medical Research Council, Cambridge, England). This clone contains an 8.0-kb *Eco*RI fragment that includes the known nonallelic Ke$^-$Oz$^-$ ($C_\lambda 2$) and Ke$^-$Oz$^+$ ($C_\lambda 3$) genes and the flanking sequences (20). We subcloned a 700-base-pair (bp) *Bgl* II–*Eco*RI fragment containing only the Ke$^-$Oz$^-$ $C_\lambda 3$ gene (Fig. 1), and this C_λ probe cross-hybridizes with all the other C_λ-like genes (20). It was radioactively labeled with [α-^{32}P]dCTP by nick-translation (27) and was used to screen the LY67 phage library.

Subcloning and Sequencing Strategies. One clone, LY67 C$_\lambda$3-6 (Fig. 1), was shown to contain $C_\lambda 3$ to $C_\lambda 6$. Appropriate subclones were made in pUC vectors (29). Nucleotide sequence analysis was carried out by dideoxy chain-termination procedures (30) in M13 vectors (31) by deploying exonuclease III–nuclease S1 methods (32) or directed sequencing using known restriction enzyme sites.

Oligonucleotide Synthesis and Hybridization. A 19-mer oligonucleotide 5′ GTGTTCGGCGGAGGGACCA 3′ corresponding to part of the $J_\lambda 3$ gene segment sequence (this paper and ref. 28) was synthesized, radiolabeled, and hybridized to the LY67 C$_\lambda$3-6 clone to search for other J_λ segments. Low-stringency washes were carried out at room temperature.

RESULTS

Rearrangement of a V_λIII Subgroup Gene to $J_\lambda 3$ in the LY67 Cell Line. One clone (LY67 C$_\lambda$3-6) containing a 18-kb piece of genomic DNA was isolated and characterized. A restriction map of this clone is shown in Fig. 1. Comparison of this map with one previously published (20) suggested that this clone contains four C_λ genes, namely $C_\lambda 3$ to $C_\lambda 6$. The sequence of the 5′ end of the LY67 C$_\lambda$3-6 clone shows that a V_λ gene rearrangement has occurred, joining this gene to the $J_\lambda 3$ gene segment, which is located 1.5 kb upstream of C$_\lambda$3 (28). Fig. 2*A* shows the partial nucleotide sequence of the rearranged V_λ in LY67 and that of a V_λ gene assigned to the V_λIII subgroup and isolated from the Burkitt lymphoma cell line PA682 (28).

Abbreviations: C, constant; J, joining; V, variable; Ke, Kern.

*The sequences reported in this paper are being deposited in the EMBL/GenBank data base (Bolt, Beranek, and Newman Laboratories, Cambridge, MA, and Eur. Mol. Biol. Lab., Heidelberg) [accession nos. J03009 ($C_\lambda 4$), J03010 ($C_\lambda 5$), and J03011 ($C_\lambda 6$)].

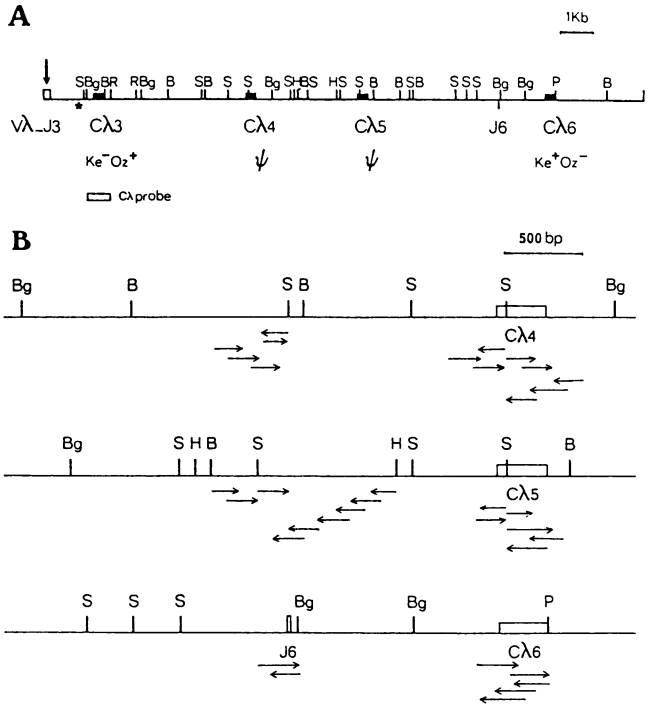

FIG. 1. (*A*) Restriction map of LY67 C_λ3-6 clone. (*B*) Sequencing strategy. B, *Bam*HI; Bg, *Bgl* II; H, *Hin*dIII; R, *Eco*RI; S, *Sst* I. Of the *Pst* I sites (P), only the one used for subcloning the fragment containing the $C_\lambda6$ gene is indicated. The rearrangement V-$J_\lambda3$ is indicated by an arrow (V, variable region). An asterisk shows the location of a polymorphic *Bam*HI site present in PA682 DNA (28) but absent from our LY67 clone.

The deduced amino acid sequence of the rearranged V gene of LY67 is also compared to the V region of the protein DEL of the subgroup V_λIII (33, 34). A 75% sequence identity indicates that the V_λ gene rearranged in LY67 is a member of the V_λIII subgroup gene family, and this is in agreement with the detection of a transcript hybridizing to a V_λIII probe in the LY67 cell line (28). The $J_\lambda3$ segment of the LY67 C_λ3-6 clone, compared to the $J_\lambda3$ segment rearranged in PA682, shows two nucleotide differences (one of them resulting in a valine/leucine amino acid substitution) that may be due to allelic polymorphism. Two other nucleotide differences are observed at the V–J junction and are probably explained by a flexibility in the mechanism by which junctions occur (35, 36).

$C_\lambda6$ Encodes a Ke^+Oz^- Chain. Fig. 2*B* shows the nucleotide sequence of the $C_\lambda6$ gene and the encoded amino acid sequence (106 residues). The residues Ala, Ser, and Thr, found, respectively, at codons 6, 8, and 57 (positions 112, 114, and 163 according to ref. 34) indicate that $C_\lambda6$ encodes a Mcg^- protein. Arg (codon 83, position 190) corresponds to the Oz^- marker, whereas Gly (codon 46, position 152) characterizes the Ke^+ marker. Therefore the $C_\lambda6$ gene encodes the fourth isotype Ke^+Oz^-.

$J_\lambda6$ Segment Is 1.5 kb Upstream of $C_\lambda6$. Only the $J_\lambda1$ (22) and $J_\lambda3$ segments (ref. 28 and this paper) have been characterized; they have been localized in genomic DNAs at 1.5 kb upstream of the respective C_λ coding regions. We therefore used an oligonucleotide corresponding to the $J_\lambda3$ sequence (see *Materials and Methods*) to search for homologous J_λ segments in the LY67 C_λ3-6 clone. As expected, a strong signal was obtained for the $J_\lambda3$-containing fragments, whereas a weaker signal allowed us to detect the $J_\lambda6$ segment in a *Sac* I–*Bgl* II fragment upstream of $C_\lambda6$. The sequence of this $J_\lambda6$ segment (Fig. 2*C*) showed that it encodes 12 amino acids (among them the characteristic Phe-Gly-Xaa-Gly residues) and that it also possesses the canonical heptamer and nonamer sequences essential to V–J rearrangement (37, 38). No signal corresponding to the putative $J_\lambda4$ and $J_\lambda5$ segments could be detected in the LY67 C_λ3-6 clone by using either the oligonucleotides ($J_\lambda3$ probe) or the genomic *Sac* I–*Bgl* II fragment ($J_\lambda6$ probe), indicating that if these segments exist their homology is too weak to be detected in our conditions of hybridization. Since the $J_\lambda3$ and $J_\lambda6$ gene segments are 1.5 kb upstream of their respective coding regions, we subcloned fragments located, respectively, at about the same distance upstream of $C_\lambda4$ and $C_\lambda5$. Although in both cases, we detected some conserved heptamer sequences, we did not

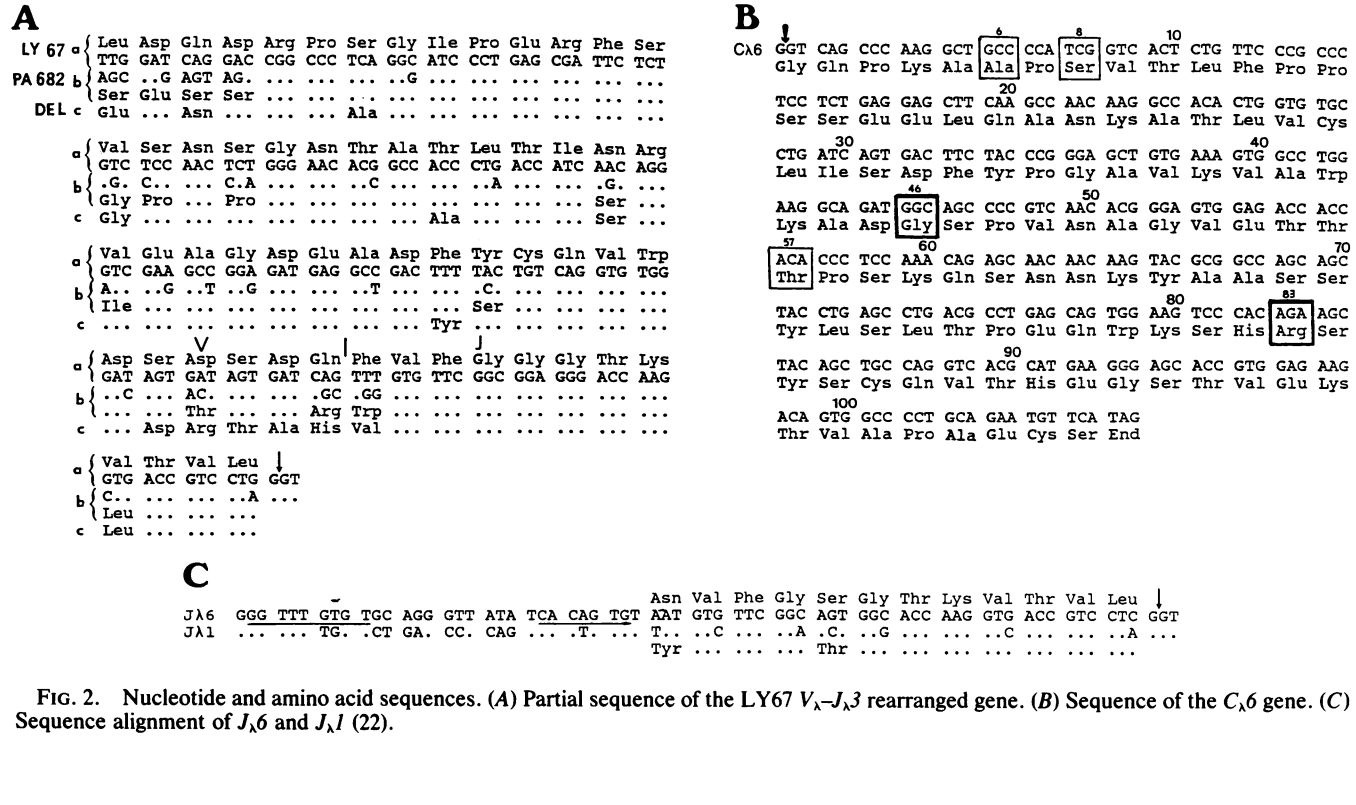

FIG. 2. Nucleotide and amino acid sequences. (*A*) Partial sequence of the LY67 V_λ–$J_\lambda3$ rearranged gene. (*B*) Sequence of the $C_\lambda6$ gene. (*C*) Sequence alignment of $J_\lambda6$ and $J_\lambda1$ (22).

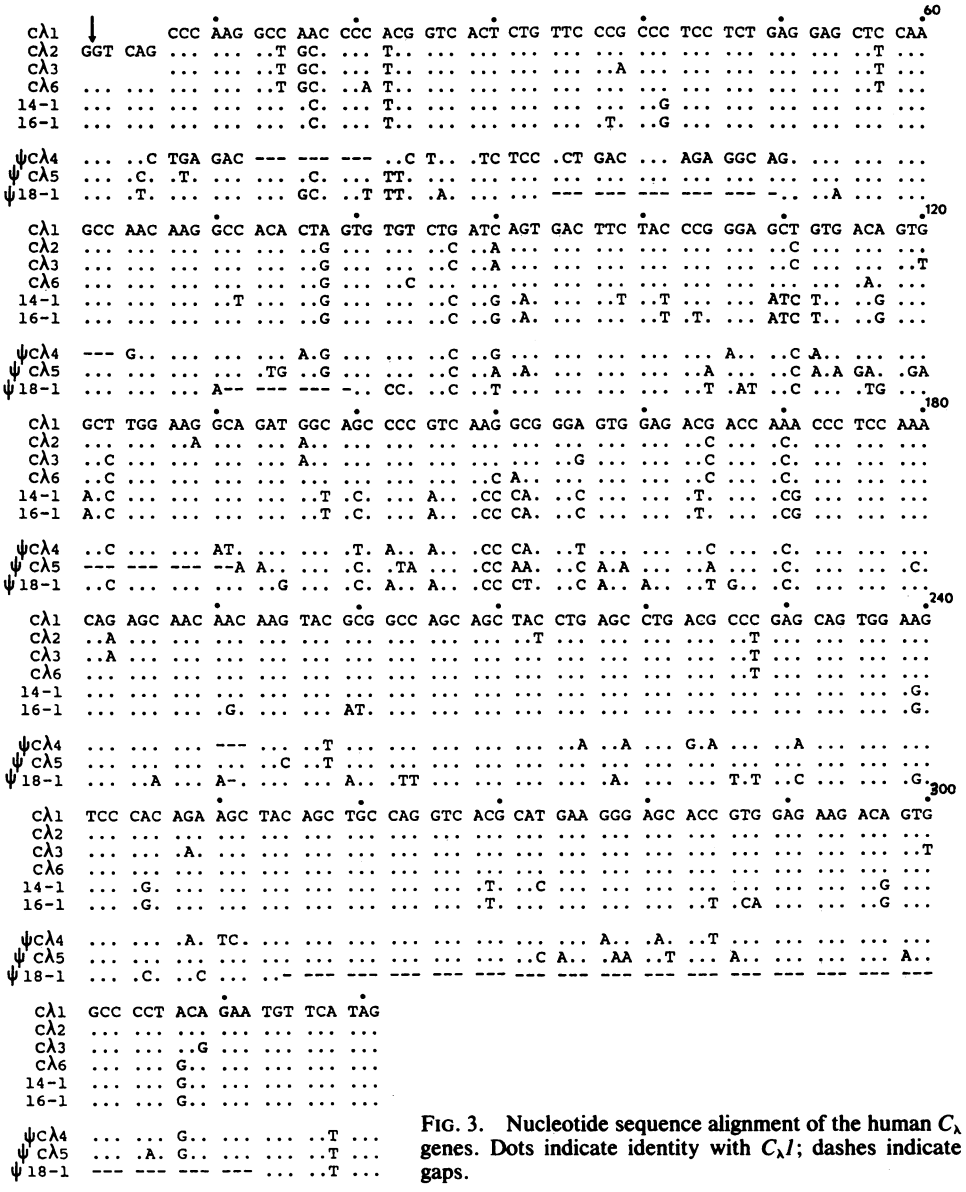

FIG. 3. Nucleotide sequence alignment of the human C_λ genes. Dots indicate identity with $C_\lambda 1$; dashes indicate gaps.

find the characteristic Phe-Gly-Xaa-Gly residues or the expected splice site at a downstream position. It is possible that the heptamer sequences are attached to poorly conserved pseudo J_λ segments and we cannot exclude the possibility that the putative $J_\lambda 4$ and $J_\lambda 5$ are localized in fragments that were not sequenced, upstream of the $C_\lambda 4$ and $C_\lambda 5$ genes.

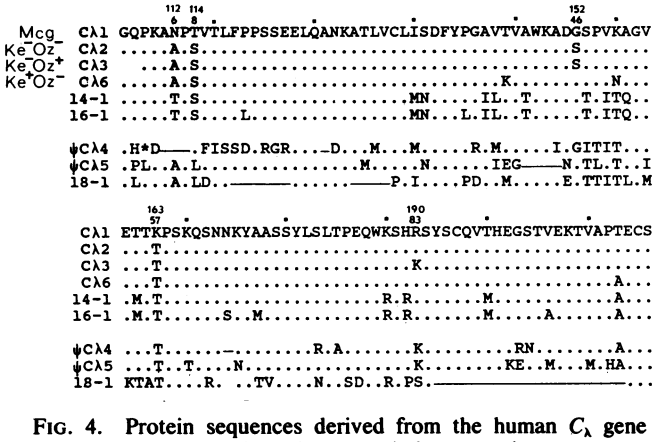

FIG. 4. Protein sequences derived from the human C_λ gene sequences. The standard one-letter symbols are used.

$C_\lambda 4$ and $C_\lambda 5$ Are Pseudogenes. Nucleotide sequences and the encoded amino acid sequences of $C_\lambda 4$ and $C_\lambda 5$ are shown in Figs. 3 and 4. Both genes are pseudogenes; the third codon of $C_\lambda 4$ is a stop codon, and $C_\lambda 4$ displays three deletions. The first deletion of 9 bp spans codons 5 to 7 and the other two deletions excise codons 21 and 64. $C_\lambda 5$ has an 11-bp deletion (codons 41–44) resulting in a frameshift.

Table 1. Amino acid differences between the four nonallelic forms of the human C_λ regions

		Amino acid residue				
Isotype	Gene	112 (6)	114 (8)	152 (46)	163 (57)	190 (83)
Mcg^+ Ke^+Oz^-	$C_\lambda 1$	Asn	Thr	Gly	Lys	Arg
Mcg^- Ke^-Oz^-	$C_\lambda 2$	Ala	Ser	Ser	Thr	Arg
Mcg^- Ke^-Oz^+	$C_\lambda 3$	Ala	Ser	Ser	Thr	Lys
Mcg^- Ke^+Oz^-	$C_\lambda 6$	Ala	Ser	Gly	Thr	Arg

Residue numbering is according to ref. 34; parentheses enclose numbering of the codons in the C_λ genes.

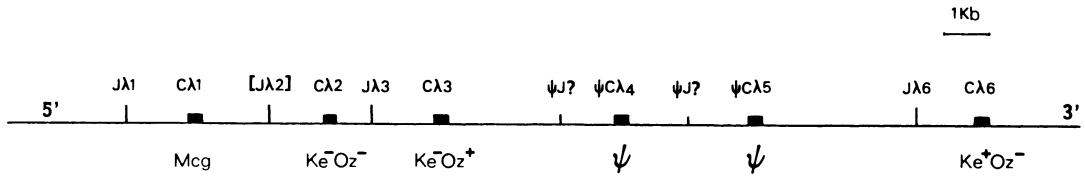

FIG. 5. Physical map of the human λ light chain C region. $C_\lambda 1$, $C_\lambda 2$, and $C_\lambda 3$ correspond, respectively, to the nonallelic Mcg, Ke^-Oz^-, and Ke^-Oz^+ chains (ref. 20; see Table 1). $C_\lambda 4$ and $C_\lambda 5$ are pseudogenes (ψ), whereas $C_\lambda 6$ encodes a Ke^+Oz^- chain. $J_\lambda 1$ (22), $J_\lambda 3$ (ref. 28 and this paper), and $J_\lambda 6$ (this paper) have been localized 1.5 kb upstream of $C_\lambda 1$, $C_\lambda 3$, and $C_\lambda 6$, respectively. $J_\lambda 2$ has not yet been localized in genomic DNA. No J_λ gene segment has so far been identified upstream of $C_\lambda 4$ and $C_\lambda 5$.

DISCUSSION

In human λ chain C regions, the Mcg marker involves amino acid residues at positions 112, 114, and 163 (numbering according to ref. 34; Table 1) corresponding, respectively, to codons 6, 8, and 57 of the C_λ genes. Mcg^+ proteins have residues Asn-112, Thr-114, and Lys-163, whereas Mcg^- proteins have residues Ala, Ser, and Thr, respectively, at these locations. However, the recently sequenced Mor protein is different from the other Mcg^- proteins by having Ala-163 instead of Thr-163 (16). The Ke and Oz markers occur at positions 152 and 190, respectively: Ke^+ proteins have Gly-152 and Ke^- have Ser-152; Oz^+ proteins have Lys-190 and Oz^-, Arg-190. These markers define four nonallelic forms of human λ chain C regions (Mcg, Ke^-Oz^-, Ke^-Oz^+, and Ke^+Oz^-), which are encoded, respectively, by the $C_\lambda 1$, $C_\lambda 2$, $C_\lambda 3$ (20), and $C_\lambda 6$ (this paper) genes (Fig. 5).

In Fig. 6, monoclonal Bence Jones proteins have been assigned as products of the C_λ genes 1, 2, 3, or 6 on the basis of the presence or absence of residues characteristic for the Mcg, Ke, and Oz markers. In most cases, there is complete concordance between the protein and the deduced amino acid sequence of the corresponding C_λ gene. However, other amino acid changes have been found in several proteins (Table 2 and Fig. 6). Since these substitutions have been noted only once, they could represent allotypic differences. However, it is not excluded that some of the proteins Ke^-Oz^- could be encoded by a C_λ gene resulting from the duplication of the $C_\lambda 2$–$C_\lambda 3$ region, as has been described in some individuals (21). In such cases these sequences should represent new isotypic differences due to the presence of several nonallelic copies of $C_\lambda 2$ gene. Differences observed in the $J_\lambda 2$ sequences (Fig. 6) might for the same reason be either allotypic or isotypic. Differences in the $J_\lambda 1$ segment region might represent allotypic differences, although the presence of not yet identified other $J_\lambda 1$ segments cannot be ruled out.

Table 2. Sequence variations in the C region of human λ chains

Isotype	Common amino acid	Residue number	Variant amino acid	Protein	Ref.
Mcg	Lys	156	Glu	WEIR	8
Ke^-Oz^-	Lys	129	Glx	CH	9
			Arg	NIG68	10
			Ser	ATK	11
	Ala	143	Val	MZ	12, 13
	Val	155	Ile	HIL	14
	Lys	156	Glu	SA	11
	Ala	157	Val	WAY	1
	Lys	172	Asn	MZ	12
			Arg	MOR	16
	Lys	187	Gln	ATK	11
	Gln	195	Leu	NIG68	10
Ke^-Oz^+	Asp	151	Glu	EV	15

Residue numbers according to Kabat *et al.* (34).

If we compare the deduced amino acid sequence of $C_\lambda 6$ gene with two known Ke^+Oz^- proteins that have identical C_λ coding regions, SM (53) and Kern (52), the protein predicted for $C_\lambda 6$ shows three differences: (*i*) lysine at position 145 (codon 39) instead of threonine, (*ii*) asparagine at position 156 (codon 50) instead of lysine, and (*iii*) alanine at position 212

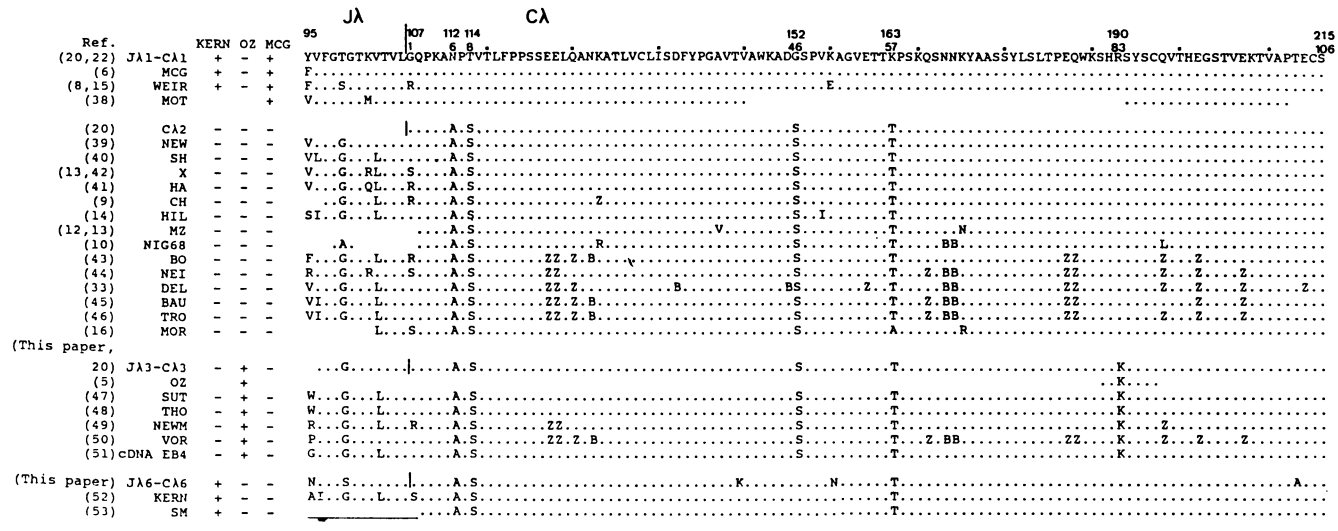

FIG. 6. Sequences of C regions of human λ chains. The protein sequences encoded by the four "active" C_λ genes and associated J_λ gene segments are compared with the λ protein C regions. The numbering of the C_λ region amino acids is according to ref. 34—e.g., positions 169, 201, and 202 are excluded in the C_λ sequences for purposes of alignment with human C_κ chains. For an easier alignment, the J_λ and C_λ gene segments are considered as being spliced and a vertical line is drawn to indicate the V–J junction. The horizontal line in the SM sequence shows a deletion.

(codon 103) instead of threonine (Fig. 6). These differences may represent allotypic variations, although we cannot entirely exclude the possibility that these different Ke^+Oz^- sequences are encoded by nonallelic genes. More sequences of C_λ genes or λ proteins should help estimate the extent of the human λ chain polymorphism.

Note Added in Proof. The $J_\lambda 2$ gene segment has recently been localized upstream of $C_\lambda 2$ (54).

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