Expression Frequency of the Human Immunoglobulin λ Light Chain Genes and the Roles of Their Recombination Signal and Spacer Sequences

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1 Introduction

The recombination signal sequences (RSS) is the essential element for the immunoglobulin gene rearrangement. The RSS consists of 3 elements: heptamer (7mer), 12-bp or 23-bp spacer, and nonamer (9mer). The heptamer and nonamer are well conserved [6]. The rearrangement occurs between an RSS with 12 bp spacer sequences and an RSS with 23 bp spacer sequences (the '12/23 rule') [1]. RSSs of indispensable V gene segments should be well conserved to maintain high efficiency of the V(D)J joining.

In this work, the RSSs of the human immunoglobulin λ light chain genes were investigated how the recombination and expression frequencies of the genes are influenced by the RSSs. We first conducted an extensive database search to estimate expression frequencies of the variable region gene for the λ light chain (V_λ) combination with the joining (J) and constant (C) region.

The genes for the λ light chain genes located on chromosome 22q11 have been sequenced recently by two different groups [4, 7]. In this one-megabase long locus, Kawasaki *et al.* [4] reported that there are 36 functional V_λ gene segments and 33 pseudogene segments, followed by 7 $J_\lambda C_\lambda$ gene segments, four of which are functional. On the other hand, Williams *et al.* reported that there are 37 V_λ gene segments, 30 of which are functional. The differences between these two reports are probably due to allelic variations.

2 Results

Fig. 1 shows the important nucleotides of RSS of the V_λ gene segment. The 1st, 2nd, 3rd, and 7th nucleotides in the heptamer and the 1st, 6th, 7th, and 8th nucleotides in the nonamer are highly conserved among the expressed segments, indicating that those bases are crucial for recombination efficiency, which is consistent with previously reported results of laboratory experiments [2, 3, 5]. Unexpectedly, however, the 15th, 16th, 17th, and 18th nucleotides in the 23bp spacer are well conserved, suggesting that the spacer sequence also plays an important role in the recombination process in the λ light chain gene.

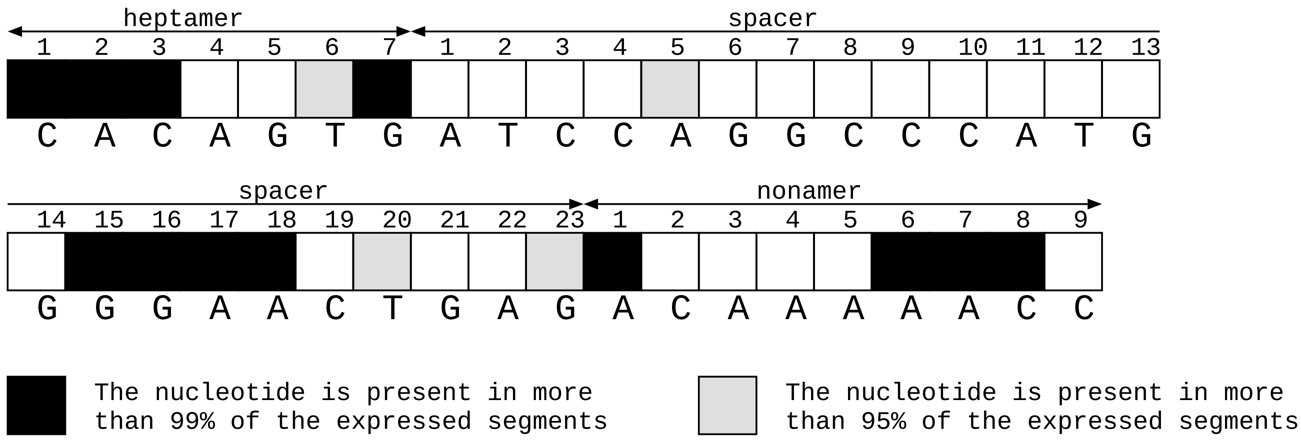

Figure 1: The conservation of the RSS of V_λ gene segments.

3 Conclusion

We have shown that, besides the heptamer and the nonamer, the spacer sequence also plays an important role in the VJ joining of human immunoglobulin λ genes. Specifically, it is suggested that the second half of the 23-bp spacer sequence affect joining efficiency because the nucleotide sequence of this region is well conserved among all RSSs, and because the V_λ segments substituted at one of these nucleotides are expressed in significantly lower frequencies.

References

[1] Bogue, M. and Roth, D.B., Mechanism of V(D)J recombination, *Curr. Opin. Immunol.*, 8:175–180, 1996.

[2] Cuomo, C.A., Mundy, C.L. and Oettinger, M.A., DNA Sequence and Structure Requirements for Cleavage of V(D)J Recombination Signal Sequences, *Mol. Cell. Biol.*, 16:5683–5690, 1996.

[3] Hesse, J.E., Lieber, M.R., Mizuuchi, K., and Gellert, M., V(D)J recombination: a functional definition of the joining signals, *Genes Dev.*, 3:1053–1061, 1989.

[4] Kawasaki, K., Minoshima, S., Nakato, E., Shibuya, K., Shintani, A., Schmeits, J.L., Wang, J., and Shimizu, N., One-Megabase Sequence Analysis of the Human Immunoglobulin λ Gene Locus, *Genome Res.*, 7:250–261, 1997.

[5] Ramsden, D.A., McBlane, J.F., van Gent, D.C., and Gellert, M., Distinct DNA sequence and structure requirements for the two steps of V(D)J recombination signal cleavage, *Embo J.*, 15:3197–3206, 1996.

[6] Tonegawa, S., Somatic generation of antibody diversity, *Nature*, 302:575–581, 1983.

[7] Williams, S.C., Frippiat, J.P., Tomlinson, I.M., Ignatovich, O., Lefranc, M.P., and Winter, G., Sequence and Evolution of the Human Germline V_λ Repertoire, *J. Mol. Biol.*, 264:220–232, 1996.