Genetic Characterization of a Human Endogenous Retroviral Element Located on Chromosome 18q21*

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A. Introduction

A substantial portion of the human genome is thought to have been generated by reverse flow of genetic information from RNA into DNA. Sequence information transposed in this manner has been given the general term "retroposon". Some retroposons show distinct structural and sequence similarities to animal retroviruses. These represent a wealth of retroviral information within the human genome, and inherent regulatory sequences may allow them to effect expression of cellular genes. We have recently discovered a new family of human retroviral sequences by hybridizing human DNA under low-stringency conditions with various DNA probes from the genome of the simian sarcoma-associated virus SSAV [1]. Here we present the structure and chromosomal localization of the human SSAV-related endogenous retroviral element S71.

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B. Results

The restriction map and genomic organization of molecular clone S71 is shown in Fig. 1. S71 is an incomplete provirus of about 6 kb with sequences related to the SSAV gag and pol genes. Sequence analysis revealed a 535-nucleotide sequence located directly adjacent to the S71 pol region with all salient features of a retroviral long-terminal repeat (LTR). The U3 region of this LTR-like structure contains signal sequences associated with the initiation and termination of transcription.

An S71 probe comprising the pol-LTR region was used for Southern blot analysis of DNA from 13 Chinese hamster × human hybrid cell lines and for in situ hybridization of human metaphase chromosomes. As illustrated in Fig. 2, S71 mapped to chromosome 18 band q21, which also contains the *yes*-1 protooncogene [2] and *bcl*-2, the major breakpoint cluster region of t(14; 18) chromosome translocations [3, 4]. Another human endogenous retroviral sequence, ERV1, has also been mapped to chromosome 18, but more distal, in bands 18q22-qter [5].

Figure 3 shows the hybridization pattern of *Bgl*II and *Eco*RI restricted genomic DNA from nine unrelated European individuals after hybridization with an S71 fragment containing the pol-LTR region. It is evident that the S71 locus shows a restriction fragment length polymorphism (RFLP) for *Bgl*II and *Eco*RI. Both RFLPs comprise two allelic fragments of 13.5 and 6.8 kb (*Eco*RI) and of 11.0 and 6.8 kb (*Bgl*II). The respective frequencies are listed in Table 1.

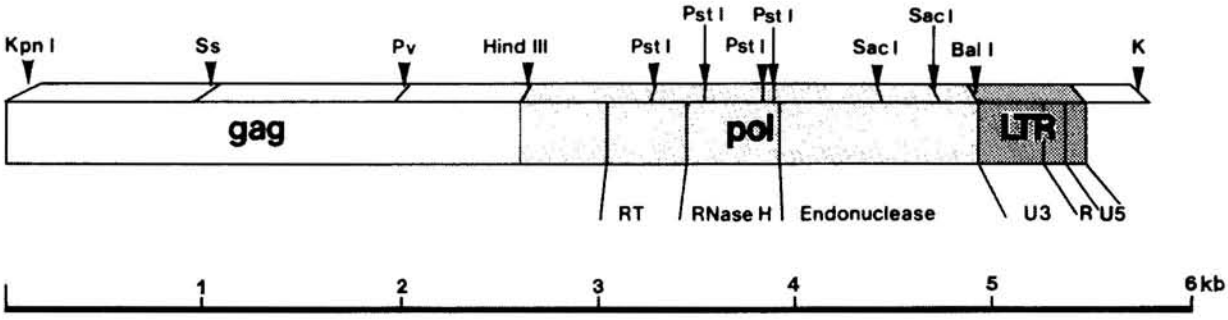

Fig. 1. Genomic organization of human endogenous retroviral element S71

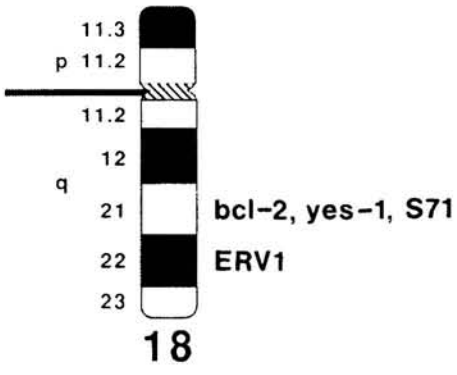

Fig. 2. Chromosomal localization of S71

Table 1. Restriction fragment length polymorphisms detected with S71 in human DNA

Restriction enzyme	Number of DNAs	Allelic fragments (kb)	Frequency
*Eco*RI	14	13.5	0.79
		6.8	0.21
*Bgl*II	9	11.0	0.61
		6.0	0.39

C. Discussion

Endogenous retroviruses and retroviral elements have been detected in the DNA of many vertebrate species, including primates. Although most of them are defective, they represent a reservoir of viral genes which may be activated spontaneously, by recombination events, or by radiation and chemical agents. Once activated, endogenous retroviruses can induce hematopoietic proliferative dis-

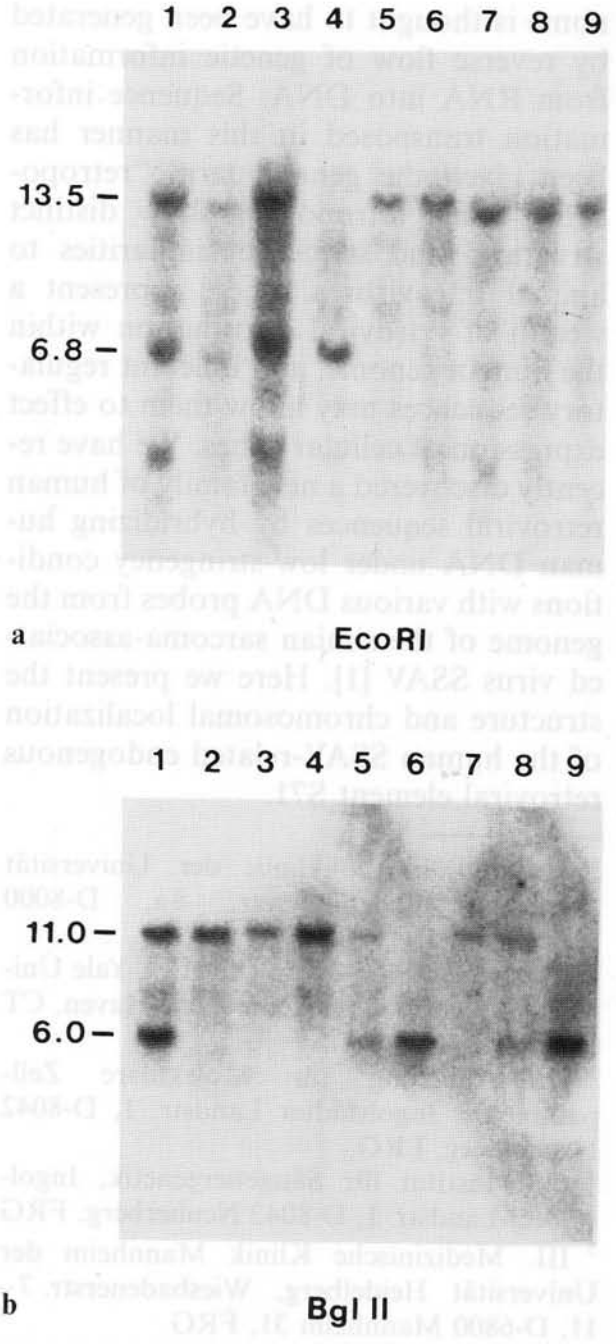

Fig. 3a, b. Restriction fragment length polymorphisms in human DNA detected with S71. EcoRI-(a) and Bgl II-digested DNA (b) from nine unrelated individuals was hybridized with a 3 kb S71 pol-LTR-subfragment

eases, e.g., by LTR-directed transcription of adjacent cellular oncogenes [6].

The human endogenous retroviral element S71 is located in a region of high biological significance. T(14; 18) translocations are observed in more than 80% of human follicular B-cell lymphomas and in about 40% of diffuse B-cell lymphomas [7]. This raises the possibility of an involvement of S71 in the genesis of neoplastic diseases. S71 has many closely related sequences dispersed throughout the human genome. These could be sites for recombination events leading to chromosomal rearrangements, as demonstrated recently for *Alu*repeats [8]. Furthermore, the LTR-like sequence in S71 contains signal sequences essential for transcriptional control. Thus, the S71 LTR could play a role in *cis*-acting mechanisms suggested to be involved in the altered transcription of the *bcl*-2 gene as a consequence of t(14; 18) translocation [9]. Since two RFLPs can be detected in human DNA using an S71 fragment as a hybridization probe, this retroviral sequence should prove to be a highly informative marker for this genomic locus.

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