Zoological Studies **39**(2): 138-143 (2000)

Zoological Studies

The ETS/IGS Region in a Lower Animal, the Seawhip, *Junceella fragilis* (Cnidaria: Anthozoa: Octocorallia): Compactness, Low Variation and Apparent Conservation of a Pre-rRNA Processing Signal with Fungi

Chaolun Allen Chen[1,*] David J. Miller[2], Nuwei Vivian Wei[1,3,4], Chang-Feng Dai[3] and Hsiao-Pei Yang[3]

[1]*Institute of Zoology, Academia Sinica, Nankang, Taipei, Taiwan 115, R.O.C.*
[2]*Department of Biochemistry and Molecular Biology, James Cook University, Townsville, Queensland 4811, Australia*
[3]*Institute of Oceanography, National Taiwan University, Taipei, Taiwan 106, R.O.C.*
[4]*Department of Biology, Chinese Culture University, Taipei, Taiwan 111, R.O.C.*

(Accepted February 10, 2000)

Chaolun Allen Chen, David J. Miller, Nuwei Vivian Wei, Chang-Feng Dai and Hsiao-Pei Yang (2000) The ETS/IGS region in a lower animal, the seawhip, *Junceella fragilis* (Cnidaria: Anthozoa: Octocorallia): compactness, low variation and apparent conservation of a pre-rRNA processing signal with fungi. *Zoological Studies* **39**(2): 138-143. We determined the nucleotide sequence of an atypically short intergenic spacer/external transcribed spacer (IGS/ETS) region in the seawhip, *Junceella fragilis*, and identified an 8-bp motif at the 5'-ETS/*18S* rDNA boundary closely resembling a fungal pre-rRNA A1 cleavage signal. This apparent conservation of processing signals was unexpected, as no corresponding sequence has previously been reported in any animal. The *J. fragilis* IGS sequence lacks repetitive motifs of the type typical of higher animals, but a microsatellite is present in the putative 3'-ETS. Comparisons of the IGS between geographically isolated populations of *J. fragilis* indicate an unexpected lack of sequence variation.

Key words: IGS, ETS, rRNA processing, Cnidaria, Lower animals.

In higher organisms, rRNA transcription units are generally arranged as tandem repeats. The primary transcript generated by RNA polymerase I contains 3 of the 4 rRNAs (18S, 5.8S, and 28S) flanked by an external transcribed spacer (ETS) and it is separated by internal transcribed spacer (ITS) regions that contain the information required for processing. The space between the 3'-end of one rDNA transcription unit and the 5'-end of the next transcription unit is known as the intergenic spacer (IGS) region, and is generally in the range of 2.5 to 30 kb in animals and plants. The spacer region performs a variety of functions — it contains termination sequences for one transcription unit and the promoter of the next, as well as enhancers (reviewed in Reeder 1989, Sollner-Webb and Mougey 1991). In vertebrates at least, it serves to insulate transcription units, in the sense that the region may bear functional similarity to insulator elements by virtue of its ability to insulate a promoter from the influence of an enhancer in a position-dependent manner (Robinett et al. 1997). Enhancer and insulator functions are attributed to repetitive motifs that occur within the IGS. The rDNA is subject to concerted evolution, such that the transcribed region is rapidly homogenized within a freely interbreeding unit (a species or population). However, the IGS is frequently heterogeneous within populations, and individuals may contain several distinct variants. For example, 3 to 9-kb-length polymorphism can exist in single *Xenopus laevis* individuals (Wellauer et al. 1974). Heterogeneity of this type presumably arises as a result of

*To whom correspondence and reprint requests should be addressed. Tel: 886-2-27899549. Fax: 886-2-27858059. E-mail: cac@gate.sinica.edu.tw.

unequal crossing-over due to the repetitive nature of much of this region (Dover et al. 1993).

While some features of IGS function are relatively well understood, the evolution of function in this region is not, neither is it clear whether patterns of variation seen in advanced animals also apply to lower animals. The process of analysis of IGS function and evolution is complicated by the fact that this region is typically large and complex in higher animals — at around 30 kb in human (Gonzalez and Sylvester 1995). However, the IGS appears to be much shorter in some lower animals. No sequence data are available for this region in any cnidarian, but in the scleractinian coral, *Pavona cactus*, the IGS is approximately 2.5 kb, and restriction digestion patterns are consistent with an internally repetitive structure like that characteristic of higher animals (Smith et al. 1997). In the process of examining several cnidarians, we discovered an atypically short IGS region in the seawhip, *Junceella fragilis*, the complete sequences of which we have determined for several individuals from 2 isolated populations. This is the first complete IGS sequence for any cnidarian, and with a size estimated at approximately 800 bp, it is the shortest IGS region identified in any animal. Comparison with sequence databases allowed us to assign the positions of the *28S* and *18S* boundaries, and identify an 8-bp motif at the 5'-ETS/*18S* rDNA boundary strongly resembling the corresponding fungal (pre-rRNA A1) cleavage signal. This apparent conservation of processing signals was unexpected, as no corresponding sequence has previously been reported in any animal. The *J. fragilis* IGS sequence lacks repetitive motifs of the type typical of higher animals, but a microsatellite is present in the putative 3'-ETS. Comparison of the IGS between geographically isolated populations of *J. fragilis* indicates an unexpected lack of sequence variation. The compactness of this region should facilitate the determination of patterns of IGS evolution in lower animals, and the identification of functional elements.

MATERIALS AND METHODS

Sample collection

Samples of *Junceella fragilis* were collected from Lutao (Green Island), an island off southeastern Taiwan (22°39'N, 121°27'E), and from Magnetic Island off the northeastern coast of Australia (19°15'S, 146°50'E) by scuba diving. A small fragment was clipped from the tip of a colony, placed in a labeled bag, and frozen in liquid nitrogen or dry ice for transfer to the laboratory. Samples were stored at –70 °C prior to analysis.

Extraction and purification of seawhip DNA

DNA extraction was essentially as described by Chen et al. (1995) and Smith et al. (1997) with slight modification. Seawhip tissue was ground into a fine powder in liquid nitrogen and transferred to 1.5 ml of DNA extraction buffer (0.4 M NaCl, 200 mM EDTA, pH 8.0). Proteinase K was then added to the sample to a final concentration of 0.1 mg/ml, and samples incubated at 55 °C for 3 to 4 h. A 1/8 volume of 5 M NaCl and a final concentration of 1% CTAB (Fluka) were then added, and incubated at 65 °C for a further 10 min. After centrifugation at 3000 rpm for 10 min, the supernatant was extracted with equal volume of phenol 2 or 3 times, until the interface became clear. The samples were then extracted with phenol/chloroform, and DNA was precipitated overnight at –20 °C with absolute ethanol and 0.3 M sodium acetate. DNA was resuspended in 50-µl aliquots of water and stored at –20 °C.

rDNA amplification, cloning, and sequencing

The rDNA IGS regions in *Junceella fragilis* were amplified using the "universal" primer pair, 28NF: 5'-GATTATGACT GAACGCCTCT AAGTCAGAAT CC-3' and *18S*-10B: 5'-TTACCATCGACAGTTGATAG-GGCA-3' (Smith et al. 1997). PCR was performed in a PC-9606 thermal sequencer (Corbett Research) using the following thermal cycle: 1 cycle at 95 °C (3 min); 4 cycles at 94 °C (30 s), 50 °C (1 min), and 72 °C (2 min); and 30 cycles at 94 °C (30 s), 55 °C (1 min), and 72 °C (2 min). The amplification reaction used 50 to 200 ng of template and BRL *Taq* polymerase in a 50-µl volume using the buffer supplied with the enzyme and under the conditions recommended by the manufacturer. The PCR products were initially checked by agarose (FMC Bioproducts; Rockland, Maine) electrophoresis in 0.8% gel in 1X TAE buffer. The amplified DNA was extracted once with chloroform and precipitated with ethanol at –20 °C followed by resuspension in water. PCR products were cloned using the pGEM-T system (Promega; Madison, WI) under the conditions recommended by the manufacturer. The nucleotide sequences were determined using an ABI 377 DNA sequences. The complete sequence of an IGS clone with the flanking coding region of *28S* and *18S* rDNA has been submitted to Genbank under accession number AF154670.

RESULTS AND DISCUSSION

The nucleotide sequence of an 1858-bp PCR product spanning the *Junceella fragilis* IGS is shown as figure 1. Comparison with both published secondary structures and the sequence databases identified the motif, 5'CTTGTTCTAAGATTTGT3', located at position 260-277 in the sequence shown, as the approximate position of the 3'-terminus of the 28S rRNA coding sequence. Likewise, the 5'-end of the 18S rRNA coding sequence is likely to be at position 1526. Thus in *J. fragilis*, the 3'-ETS, IGS, and 5'-ETS account for approximately 1249 bp in total.

Consideration of yeast and mouse data (Mason et al. 1997, Reeder and Lang 1997) suggests that termination of the rRNA transcript is likely to involve poly-(dT) tracts located at positions 281-290 or 488-505 in the sequence shown as figure 1. The proximity of the former to the 3'-end of the 28S rRNA implies that the latter is more likely to be functionally sig-

```
GATTATGACT GAACGCCTCT AAGTCAGAAT CCGTGCTAGA AGCAACGAT TCATTCCTCT GGACAATCTT   70
AGGCGAACGA GAATAGAAGC TTCGGCTTCC TGCGTCACAA TGTGCTAAGG AGCAGACTAC GCTCTGAAGC  140
ACTACCTTGA CCAAAATCTA AATTTTCCAG AGCTAAATCC TTTGCAGACG ACTTAAATAA AGAACGGGGT  210
ATTGTAAGCG GTAGAGTAGC CTTGTTGCTA CGATCCGCTG AGATTAAGCC CTTGTTCTAA GATTTGTACC  280
TTTTTTTTTT CAATCTTACC GACATCCTCC TAGTTACCGT CCCTTCGCCT CGTGATGGCT TCGCACAGAC  350
GGACACACCG AGAGACCGAC ACACGCACCG ACCGACCGAC GGACCGACCG ACACACCGAC TATTGTTTTC  420
CAAGACCCCG GCATCCTCCA GGGGACCGTC GACATTCCTC GATATTCTCT TACAACATTC TTGCACGTTT  490
TTTTGCTCTT TTTTTCCATC TCGAATGATC TTTCGTCGAC GTTTATAACT GCAGAGTTGA AATCACATGA  560
AAAAAAAAGT ACTGCCGGCA CCGGTTAGGA AATCCTACAA GTGACAGGCC CGAACGGCTA AAAGGGCAAA  630
AAGCAATAAA TTCCGTGGGA ATTTCTCTCG GAATTGACAA AAATGTGCTG CATTGCACTT CCACGCATGT  700
TTTCCGTAAC GATCGACGTT CACCGCATCG TGACATCGTC CAAGGGGAGG GGGCCTCTGT ATTGATGGGG  770
CTTGCCCAGA CTTGCCTGCT AAGAAGCGTG GCCTAATTTG GGGTATCAGA CGTGGCGAGA AGTGCAGTCG  840
GTCGATGTGA GAAAAGGCAC TGACCGATGG CTACATTCGT TCGGAAGCGA TGGGGTTTGG GGAAACCGGC  910
GAACGGAAAA GAGCTCGGAT TGGTCGAGAG CCCGGAACTT ATTTTTTCGT TCCCGGTTTG TCGGGGCCCA  980
TGGTAACGCG CGATGGTTTC TCCGGCCACT TTCACCGACG TCTCCTGCCC GAAGTGGAAT GGAGCGGACT 1050
GGTGAGAAAG AATTTCTCGT GCCAGAATCC GGCCATTCTC GCTCGGATGC GTGCCAGGAG TCAGTTTATG 1120
TTTGTTCGGT CGCCTGGCGA CCGAGCTCGT TGGCGAATGT TGTACGTGTG TCCGTTGGAC AACGCTACCG 1190
AAGCAGTGTT TGCGAAGCTA TACGCTTGCT CGTTTTGTCG CGGGTACGTT TTTACTAACT TACTTACTAA 1260
GTCGAGTCAA GTTAAACGCG TGCTCGTGGC AAGAGAGACG TTGAAAGACG TGGCAAATAA AGGTTTCGGT 1330
TTGCCGAGGC ATCATCATTT GGTGAATGTC CGAGGTCGAA CCGTACGTAA AACGAGAGAA CGCACGTGCA 1400
GGCCCGTTCC CCAAACTGTT AGAGTTTGCG TGTGCGTCTC GTGAAGCGAA AAATGAGGTA CGAGCAGAGA 1470
AGCGACTTTT TGTTTCGTTT CTCTCTCTTC ACCGTGATTT TTTTTTCACG ACACTTAACT GGTTGATCCT 1540
GCCAGTAACA TATGCTTGTC TCAAAGATTA AGCCATGCAT GTCTAAGTAT AAGCACTTGT ACTGTGAAAC 1610
TGCGAATGGC TCATTAAATC AGTTATCGTT TATTTGATTG TACCTTTACT ACTTGGATAA CCGTAGTAAT 1680
TCTAGAGCTA ATACATGCGA AAAGTCCCGA CTTCCGGAAG GGATGTATTT ATTAGATTAA AAACCAATGC 1750
GGGTTCACGC CCGGCTTTTT GGTGATTCAT AATAACTCTT CGAATCGCAT GGCCTCACGC GCCGGCGATG 1820
TTTCATTCAA ATTTCTGCCC TATCAACTGT CGATGGTA
```

Fig. 1. Nucleotide sequence of the region of the *J. fragilis* rRNA transcription unit spanning the 3'-end of the *28S* rDNA, 3'-ETS, IGS, 5'-ETS and the 5'-end of *18S* rDNA. Sequences complementary to the PCR primer sequences are shown in gray text and the deduced boundaries of the *28S* and *18S* rDNA are boxed. A putative terminator sequence is underscored with a dashed line; candidate UCE and proximal promoter motifs are underscored with solid lines. The shaded boxes indicate a microsatellite in the 3'-ETS (positions #346-409) and a motif in the 5'-ETS (positions #1518-1525) showing strong identity with the corresponding region in fungi (see Fig. 2).

nificant; consistent with the function of preventing slippage by RNA polymerase I (Jeong et al. 1996), the #488-505 poly-(dT) tract is interrupted. The 3'-ETS is therefore likely to be approximately 250 bp long. Many RNA polymerase promoters are bipartite, consisting of a proximal promoter domain and an upstream control element (UCE) (Marilley and Pasero 1996). The spacing and level of identity between 5'AAG(C/T)TA(T/A)ACGC(T/G)TGCTCG-T3' motifs located at #1205-1223 and #1269-1287 in the *J. fragilis* sequence (see Fig. 1) are consistent with these being proximal promoter and UCE motifs. If these are promoter components, then transcription probably begins 20 to 30 bp downstream of the 2nd motif, leading to the prediction that the 5'-ETS region is approximately 200 bp long in *J. fragilis*.

Surprisingly, the ETS region immediately upstream of the 5'-end of the *18S* rDNA closely resembles the corresponding part of a rRNA transcription unit in a variety of fungi (Fig. 2), whereas this sequence is not conserved across the Metazoa. The mechanism by which the rRNA precursor is processed is not well characterized in metazoans. In both Metazoa and fungi, U3 snoRNA plays a critical role in defining the ends of the 18S rRNA (Hughes and Ares 1991), although in neither case is there any evidence for direct interaction at the 5'-cleavage point. Correct 18S rRNA 5'-end formation in yeast is specified by 2 independent mechanisms cleavage occurs exactly 3 bases 5'- upstream of a pseudoknot in the 18S rRNA, but is also defined independently by the conserved nucleotides in the ETS immediately 5' downstream of the 18S rRNA (Venema et al. 1995). How this sequence defines the 5'-end of the 18S rRNA is unknown, but the level of identity between *J. fragilis* and fungi in this part of the ETS implies a common processing mechanism, and points to more extensive conservation of rRNA processing systems than has previously been apparent.

No long-term repeated patterns were identified in the *J. fragilis* sequence, however, tetranucleotide microsatellites with the general form, C(A/G)GA, were identified near the 3'-end of the *28S* rDNA, within the putative 3'-ETS region (Fig. 1). In the example shown as figure 1, the region between positions 346 and 409 is a single microsatellite interrupted by the short motif, GAGA. Comparison between 27 colonies of *J. fragilis* from the same site in Taiwan indicated extensive polymorphism within this region, but almost no variation outside of it (Chen et al., unpubl. data). The extent of conservation of the *J. fragilis* IGS is most striking when sequences are compared between Taiwanese and Australian isolates; when the microsatellite is excluded from such comparisons, the sequences differ by < 4%. This may be due to the reproductive characteristics of *J. fragilis* in which local populations are formed by fragmentation (Walker and Bull 1983, Vermeire 1994). The mating system has been demonstrated to be of major importance in maintaining the amount of genetic diversity of the IGS in the weed, *Miscanthus sinensis* var. *glaber* at organismal level (Chou et al. 1999). By contrast, RFLP patterns imply much greater variation within a single patch of another anthozoan, the scleractinian coral, *Pavona cactus*, on the Great Barrier Reef (Smith et al. 1997).

The IGS is extremely short in *J. fragilis* — probably less than 800 bp if our assignments of promoter and terminator regions are correct. It is also atypical in lacking the usual internally repetitive pattern, and (with the exception of the microsatellite) shows extremely low variation. These features are presumably interrelated: length variation and heterogeneity usually result from different numbers of repeat units, but the operation of mechanisms such as unequal crossing-over requires the presence of multiple units. The IGS repeat units act as enhancers and are related in sequence to the promoter. These enhancers also act as supressors of rRNA transcription from other arrays of tandem repeats (Mougey et al. 1996); thus they are likely to be of greater significance in organisms with multiple rRNA arrays.

The tailed frog, *Ascaphus truei*, is the only organism in which the size and level of variation of the IGS are comparable with those in *J. fragilis*. In *A. truei*, the IGS is approximately 1.5 kb in size, and only minor length variation was seen among 11 individuals from 2 widely separated populations (Morgan and Middleton 1992). The similarity between *A. truei*

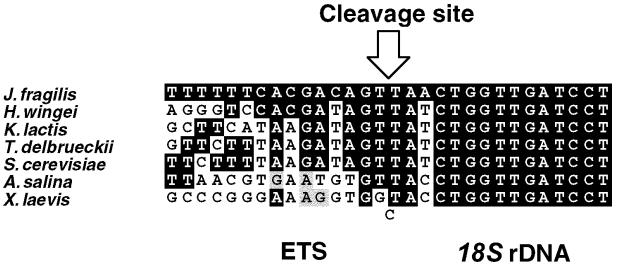

Fig. 2. Sequence surrounding the ETS/18S rRNA boundary in *J. fragilis*, aligned with the sequence at the A1 cleavage site in the fungi, *Hansenula wingei* (accession number X87403), *Kluyveromyces lactis* (X87402), *Torulaspora delbrueckii* (X87400), and *Saccharomyces cerevisiae* (X84701) and the metazoans *Artemia salina* (X05628) and *Xenopus laevis* (X02995). The ETS sequence immediately 5' upstream of the *J. fragilis 18S* rDNA closely resembles an evolutionarily conserved motif in fungi (Venema et al. 1995).

and *J. fragilis* extends to the fact that in both cases a microsatellite is present in these regions, and length variation arises largely from different numbers of repeats in the microsatellite. A significant difference is that the *A. truei* IGS contains longer-term repeat units, whereas that of *J. fragilis* does not. Searching the Genbank database has led us to conclude that microsatellites are frequently present in IGS regions, and are therefore likely to give rise to cryptic variations via several possible mechanisms (Tautz et al. 1987). We suggest that in the case of *J. fragilis* and *A. truei*, the presence of microsatellites may be responsible for the low variation seen in proximal regions. While replication slippage is thought to be the predominant mechanism by which microsatellite length variants occur at unique loci, unequal crossing-over is likely to be of greater significance when microsatellites are present in complex loci such as the rRNA arrays. The presence of a recombination hot-spot, as these microsatellites appear to be, may repress proximal crossing-over events and may be responsible for the low variation of adjacent regions. Because replication slippage and unequal crossing-over result in very different patterns of variation, characterization of the rRNA microsatellite profiles of a large number of individuals and their offspring (or gametes) should be informative with respect to the predominant mechanisms of change.

Acknowledgments: We thank the members of the Evolution and Ecology Discussion Group, Institute of Zoology, Academia Sinica, Taipei (IZAS) for constructive comments before submission. This is contribution no. 6 by the Evolution and Ecology Group, IZAS. This project is supported by both an infrastructure grant, IZAS (Taiwan) to CAC and an ARC grant (Australia) to DJM.

REFERENCES

Chen CA, DM Odorico, M ten Louis, JE Veron, DJ Miller. 1995. Systematic relationships of the Anthozoa using 5'-end of 28S rDNA. Mol. Phyl. Evol. **4:** 175-183.

Chou CH, YC Chiang, TY Chiang. 1999. Within- and between-individual length heterogeneity of the rDNA-IGS in *Miscanthus sinensis* var. *glaber* (Poaceae): phylogenetic analyses. Genome **42:** 1-6.

Dover GA, AR Linares, T Bowen, JM Hancock. 1993. Detection and quantification of concerted evolution and molecular drive. Meth. Enzymol. **224:** 525-541.

Gonzalez IL, JE Sylvester. 1995. Complete sequence of the 43 kb human ribosomal DNA repeat: analysis of the intergenic spacer. Genomics **27:** 320-328.

Hughes JMX, M Ares Jr. 1991. Depletion of U3 small nucleolar RNA inhibits cleavage in the 5' external transcribed spacer of yeast pre-ribosomal RNA and impairs formation of 18S ribosomal RNA. EMBO J. **10:** 4231-4239.

Jeong SW, WH Lang, RH Reeder. 1996. The release element of the yeast polymerase I transcription terminator can function independently of Reb1p. Mol. Cell. Biol. **15:** 5929-5936.

Mason S, M Wallisch, I Grummt. 1997. RNA polymerase I transcription termination: similar mechanisms are employed by yeast and mammals. J. Mol. Biol. **268:** 229-234.

Morgan G, KM Middleton. 1992. Conservation of intergenic spacer length in ribosomal DNA of the tailed frog, *Ascaphus truei*. Gene **110:** 219-223.

Mougey EB, LK Pape, B Sollner-Webb. 1996. Virtually the entire *Xenopus laevis* rDNA multikilobase intergenic spacer serves to stimulate polymerase I transcription. J. Biol. Chem. **271:** 27138-27145.

Reeder RH. 1989. Regulatory elements of the generic ribosomal gene. Curr. Opin. Cell Biol. **1:** 466-474.

Reeder RH, WH Lang. 1997. Terminating transcription in eukaryotes: lessons learned from RNA polymerase I. Trends Biochem. Sci. **22:** 473-477.

Robinett CC, A O'Connor, M Dunaway. 1997. The repeat organizer, a specialized insulator element within the intergenic spacer of the *Xenopus* rRNA genes. Mol. Cell. Biol. **17:** 2866-2875.

Smith C, CA Chen, HP Yang, DJ Miller. 1997. A PCR-based method for assaying molecular variation in corals based on RFLP analysis of the ribosomal intergenic spacer region. Mol. Ecol. **6:** 683-685.

Sollner-Webb B, EB Mougey. 1991. News from the nucleolus: rRNA gene expression. Trends Biochem. Sci. **16:** 58-62.

Tautz D, C Tautz, D Webb, GA Webb. 1987. Evolutionary divergence of promoters and spacers in the rDNA family of four *Drosophila* species. Implications for molecular coevolution in the multigene families. J. Mol. Biol. **195:** 525-542.

Venema J, Y Henry, D Tollervey. 1995. Two distinct recognition signals define the site of endonucleolytic cleavage at the 5'-end of yeast 18S rRNA. EMBO J. **14:** 4883-4892.

Wellauer PK, RH Reeder, D Carroll, DD Brown, A Deutch, T Higashinkagawa, IB Dawid. 1974. Amplified ribosomal DNA from *Xenopus laevi*s has heterogeneous spacer length. Proc. Natl. Acad. Sci. USA **71:** 2823-2827.

白蘆莖鞭珊瑚核醣核酸之外轉錄和基因區間：精簡、低變異與蕈類 pre-rRNA 處理序列的顯著保守

陳昭倫[1] David Miller[2] 魏汝薇[1,3,4] 戴昌鳳[3] 楊曉佩[3]

我們定序白蘆莖鞭珊瑚核醣核酸之外轉錄和基因區間的核苷酸序列，發現此區間為一條不典型的短外轉錄和基因區間序列，而且位在外轉錄區間和 *18S* 核醣核酸交界處的一組 8-bp 片段，與蕈類 pre-rRNA A1 剪切訊息序列呈現出顯著的相似性。這段處理訊息明顯的保守性在其他動物相對的序列中未曾被報導過。白蘆莖鞭珊瑚的核醣核酸基因區間序列缺少一般較高等動物同一序列中的長重複片段，但是在外轉錄區間的 3 撇端具有一組微衛星序列。比較不同地理區的白蘆莖鞭珊瑚基因區間，顯示不同族群間缺乏明顯的序列變異。

關鍵詞：基因區間，外轉錄區間，核醣核酸處理，刺絲胞動物，低等動物。

[1] 中央研究院動物研究所
[2] Department of Biochemistry and Molecular Biology, James Cook University, Townsville, Queensland 4811, Australia
[3] 國立台灣大學海洋研究所
[4] 文化大學生物系