Available online at www.sciencedirect.com
ScienceDirect
ELSEVIER
Virology 354 (2006) 217–223
VIROLOGY
www.elsevier.com/locate/yviro

Erratum to Rapid Communication

The 3′ untranslated region of tick-borne flaviviruses originated by the duplication of long repeat sequences within the open reading frame

T.S. Gritsun *, E.A. Gould

Centre for Ecology and Hydrology, Mansfield Rd., Oxford 0X1 3SR, UK

Received 7 February 2006; returned to author for revision 1 March 2006; accepted 2 March 2006

Abstract

Comparative alignment of the 3′untranslated regions (3′UTRs) of tick-borne flaviviruses has previously revealed short direct repeat sequences about 25–70 nucleotides long [Gritsun, T.S., Venugopal, K., Zanotto, P.M., Mikhailov, M.V., Sall, A.A., Holmes, E.C., Polkinghorne, I., Frolova, T.V., Pogodina, V.V., Lashkevich, V.A., Gould, E.A., 1997. Complete sequence of two tick-borne flaviviruses isolated from Siberia and the UK: analysis and significance of the 5′ and 3′-UTRs. Virus Res. 49 (1) 27–39; Wallner, G., Mandl, C.W., Kunz, C., Heinz, F.X., 1995. The flavivirus 3′-noncoding region: extensive size heterogeneity independent of evolutionary relationships among strains of tick-borne encephalitis virus. Virology, 213 (1) 169–178]. We now show that these short sequences appear to have originated from longer repeat sequences (LRSs) that are present both in the 3′UTR and the open reading frame of the genome. We propose that the 3′UTR, and possibly the open reading frame, evolved through multiple duplications, deletions and mutations of a primordial sequence element.

Keywords: Tick-borne flaviviruses; Direct repeats; Untranslated regions; 3′UTR

Introduction

The tick-borne flaviviruses (TBFV) represent one of four major ecological groups in the genus *Flavivirus* (family *Flaviviridae*) (Heinz et al., 2000). They are particularly prevalent in Europe and Russia where they cause significant morbidity and mortality (Gritsun et al., 2003). Also included in the genus are the mosquito-borne flaviviruses (MBFV), the no known vector (NKV) flaviviruses and three tentative flavivirus species, termed the non-classified flaviviruses (NCFV). The flaviviruses are small (50 nm) enveloped viruses with single-stranded positive-sense RNA genomes of about 11,000 nucleotides. The open reading frame (ORF) encodes three structural and seven non-structural proteins, the latter comprising the viral RNA polymerase complex. The ORF is flanked by untranslated regions (UTRs), 5′UTR and 3′UTR, which form complex RNA structures that interact with RNA polymerase to initiate viral RNA synthesis. The 3′ UTRs of flaviviruses (about 400–700 nucleotide long) have attracted much scientific interest because genetic modifications within these regions are known to attenuate the viruses without altering their antigenic specificity, making these regions potential targets for live-attenuated vaccines and/or for antivirals. One of the many puzzling features within the 3′UTR is the presence of short (20–70 nucleotides long) direct repeat sequences that are conserved for each flavivirus group or subgroup (reviewed in Markoff, 2003). Four R1 repeats, two R2 repeats and two R3 repeats, approximately 23, 26 and 70 nucleotides long, respectively, apparently arranged randomly, have been described in the 3′UTR of the TBFV (Wallner et al., 1995). In this paper, we demonstrate that these short repeats originate from at least six long repeat sequences (LRSs) approximately 200 nucleotides in length, arranged in tandem. Four of these LRSs are present in the 3′UTR and two in the 3′ region of the open reading frame (ORF). We propose that evolution of the 3′UTR and probably the ORF occurred through multiple duplication of LRSs that form the basis for the development of the functionally essential secondary RNA structures.

Methods and results

Initially, the 3′UTRs of all available TBFV sequences were aligned using ClustalX (Thompson et al., 1997) and the

---

DOI of original article: doi:10.1016/j.virol.2006.03.002.

* Corresponding author. Fax: +44 1865 281 696.
E-mail address: tsg@ceh.ac.uk (T.S. Gritsun).

0042-6822/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.virol.2006.03.052

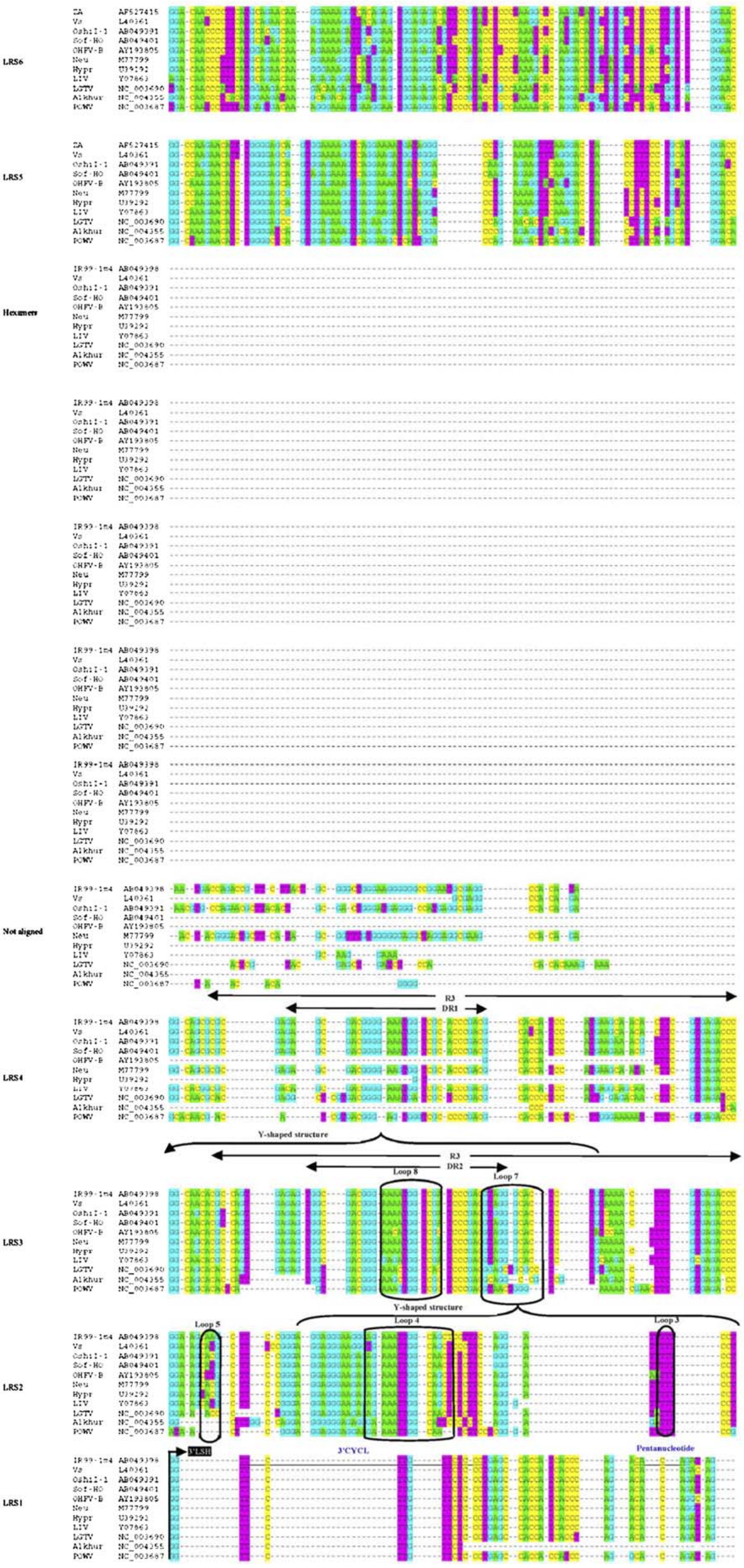
LRS6
LRS5
Hexamers
Not aligned
LRS4
LRS3
LRS2
LRS1
ZA AF527415
IR99-1m4 AB049398
Vs L40361
Oshi I-1 AB049391
Sof-HO AB049401
OHFV-B AY193805
Neu M77799
Hypr U39292
LIV Y07863
LGTV NC_003690
Alkhur NC_004355
POWV NC_003687
R3
DR1
Y-shaped structure
DR2
Loop 8
Loop 7
Loop 5
Loop 4
Loop 3
5'LSH
3'CYCL
Pentanucleotide

Fig. 1.