

GENOME WATCH

Split reality for novel tick virus

Hayley M. Bennett



This month's Genome Watch describes the discovery of a segmented RNA virus that provides an evolutionary link between segmented and unsegmented genomes.

The genomes of RNA viruses consist of either a single unit (known as unsegmented) or multiple units (known as segmented), and this arrangement is conserved within each virus family. Owing to the high level of sequence divergence between virus families, the evolutionary links between segmented and unsegmented genomes have been difficult to decipher. However, the recent discovery of a novel RNA virus provides important insights into the evolutionary relationship between segmented and unsegmented viral genomes¹.

During a screen for Huaiyangshan virus (which causes a haemorrhagic fever-like disease in humans) in ticks, Qin *et al.* unexpectedly discovered two flavivirus-like RNAs in the samples. Flaviviruses have unsegmented genomes that consist of a single ORF, which is translated into a large peptide and is subsequently cleaved by viral and cellular proteases into structural and non-structural proteins, including the NS3 and NS5 products for RNA capping and genome replication. The RNAs that were detected in the samples resembled the NS3 and NS5 RNAs and were extended using a 'genome walking' approach. Qin *et al.* observed that a virus could be propagated in insect and mammalian cell lines from the tick homogenate that contained these RNAs, so they reasoned that this was a newly discovered virus, which they named Jingmen tick virus (JMTV) after the region and host in which it was found.

Electron microscopy of infected cells showed that JMTV virions are spherical, enveloped and slightly larger than flavivirus virions. As flaviviruses contain unsegmented genomes, Qin *et al.* expected that the NS3-like

and NS5-like contigs could be joined; however, although high-throughput RNA sequencing (RNA-seq) was successfully used to extend the length of the contigs, it was not possible to join them, which suggests that JMTV is a segmented RNA virus. Other unusual features in the viral sequence hinted that it was not a typical flavivirus: both contigs were flanked by 5' and 3' UTRs and contained 3' poly(A) tails, which suggested that they were two distinct ORFs.

Using an inventive application of RNA-seq data, the authors searched for other contigs with similar expression levels to the NS3-like and NS5-like contigs. Two candidate RNAs were detected, which were absent in the tick genome and could not be amplified by direct PCR, suggesting that they are derived from a viral RNA source. Furthermore, all four contigs contained conserved 5' and 3' sequences, which provides compelling evidence that they are all segments of the same virus. The four segments together form a genome of 11,401 nucleotides, and sequence analysis confirmed that the NS3-like and NS5-like contigs encode non-structural proteins, whereas the other two contigs are predicted to encode envelope, capsid and membrane proteins. Interestingly, a BLAST search showed that one of the newly identified contigs was homologous to an unannotated transcript from the helminth parasite *Toxocara canis* (also known as dog roundworm). The authors noted that, similarly to JMTV, four highly expressed RNAs that lack a DNA form had been previously described in this parasite². Thus, the authors inferred that they were from a related virus

and named this putative virus *T. canis* larva agent (TCLA).

Strikingly, the four RNA segments of JMTV and TCLA show clear sequence similarities, and a phylogenetic analysis of the NS3-like and NS5-like sequences showed that they cluster together as a monophyletic group of the Flaviviridae, which suggests that they share a common ancestor. The evolutionary costs and benefits of segmentation are poorly understood. Computational models suggest that the shorter lengths of segmented genomes might provide an advantage in terms of genomic stability³. The JMTV virus itself seems to be relatively successful — in the Hubei province of China, the virus is prevalent in a range of different tick species and is frequently transmitted between ticks via feeding on their cattle hosts¹.

This study provides the first example of a virus with a segmented genome that is at least partly derived from an unsegmented genome. By following up their initial findings, the authors unexpectedly discovered a novel virus, and the remarkable origins of the genome suggest that we need to carefully examine the possible evolutionary routes that lead to the segmentation of virus genomes.

Hayley M. Bennett is at the Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK.

e-mail: microbes@sanger.ac.uk

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Competing interests statement

The author declares no competing interests.

