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Short communication

Identification of two severe fever with thrombocytopenia syndrome virus strains originating from reassortment

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ABSTRACT

Recently, a novel bunyavirus, severe fever with thrombocytopenia syndrome virus (SFTSV), was isolated in central China. The virus can cause multi-clinical symptoms: severe fever, thrombocytopenia, leukocytopenia, with a mortality rate of ~10%. Several studies show that SFTSV could undergo rapid evolution via gene mutation and homologous recombination. However, as an important evolutionary force for segmented-genome viruses, reassortment has not been reported in SFTSV. In this study, we identified two SFTSV strains of which the S segment has different origin from M and L, suggesting that reassortment might be potential force driving rapid change of SFTSV. This result might shed new light on the evolutionary behavior of the novel virus.

In 2009, a new emerging infectious disease broke out in central China (Xu et al., 2011; Yu et al., 2011). With a mortality of ~10% (Lam et al., 2013), its clinical symptoms are characterized by fever, gastrointestinal bleeding, thrombocytopenia, and leukocytopenia in patients (Yu et al., 2011). The disease is termed the severe fever with thrombocytopenia syndrome (SFTS) (Feldmann, 2011; Yu et al., 2011). The causing pathogen is designated as SFTS virus (SFTSV) (Yu et al., 2011) or Huaiyangshan virus (HYSV) (Chen et al., 2012; Zhang et al., 2012b,c), and identified as a novel member of the phlebovirus genus in the Bunyaviridae family (Yu et al., 2011). Except for human, the disease has not been reported in other domestic animals although SFTSV can be isolated from ticks on the surface of sheep, cattle, and dogs (Jiang et al., 2012).

The rapid change of genetic material is the basis of RNA virus evolution and adaption of the host. The single-stranded negative-sense RNA genome of SFTSV is comprised of three segments, i.e. S, M, and L segments. The segment S has two nonoverlapping open reading frames (ORFs) encoding nucleocapsid (N) and nonstructural (NS) proteins. Segment M encodes two viral envelope glycoproteins, Gn and Gs, which are involved in immunogenicity and neutralizing or protective epitopes (Elliott, 1997). Segment L encodes the RNA-dependent RNA polymerase (RdRp). Because of the absence of proofreading functions in the RdRp, SFTSV has a high mutation rate (~10^{-4} substitutions/site/year) during its replication (Lam et al., 2013), which may provide the basis of its genetic diversity (Zhang et al., 2012a). In addition, although homologous recombination is thought to be rare in negative strand RNA virus, intragenic recombination still might play a potential role in the rapid evolution of the virus (He and Ding, 2012; Zhang et al., 2011). In segmented-genome viruses, reassortment is an extremely efficient evolutionary force, which allows them to acquire many of the key adaptive mutations in a single step and hence makes a major leap in fitness space, even results in a change of host tropism (Kuiken et al., 2006). Reassortment between segments has also been reported within the vertebrate, plant or arthropod host for viruses of all genera in the *Bunyaviridae* (Webster et al., 2011). However, it is not determined whether reassortment can play a role in rapid change of SFTSV (Lam et al., 2013).

In this study, we analyzed all available SFTSV complete genome sequences, and reported two SFTSV isolates undergone different reassortment events. This finding might broaden our knowledge on molecular mechanism of the genetic diversity of SFTSV.

All complete genomes of 36 SFTSV isolates (listed in Fig. 3) were downloaded from the GenBank and aligned with CLUSTALW (Thompson et al., 1997) complemented in Mega5 (Tamura et al., 2011). According to Bayesian Information Criterion within MEGA5 software, the best-fit substitution model, General Time Reversible (GTR) model was chosen for Maximum-Likelihood (ML) phylogenetic analysis. Based on the sequence alignment of each segment, Neighbor-Joining (NJ), Maximum Parsimony (MP), and ML methods were employed to reconstruct the phylogenetic history of

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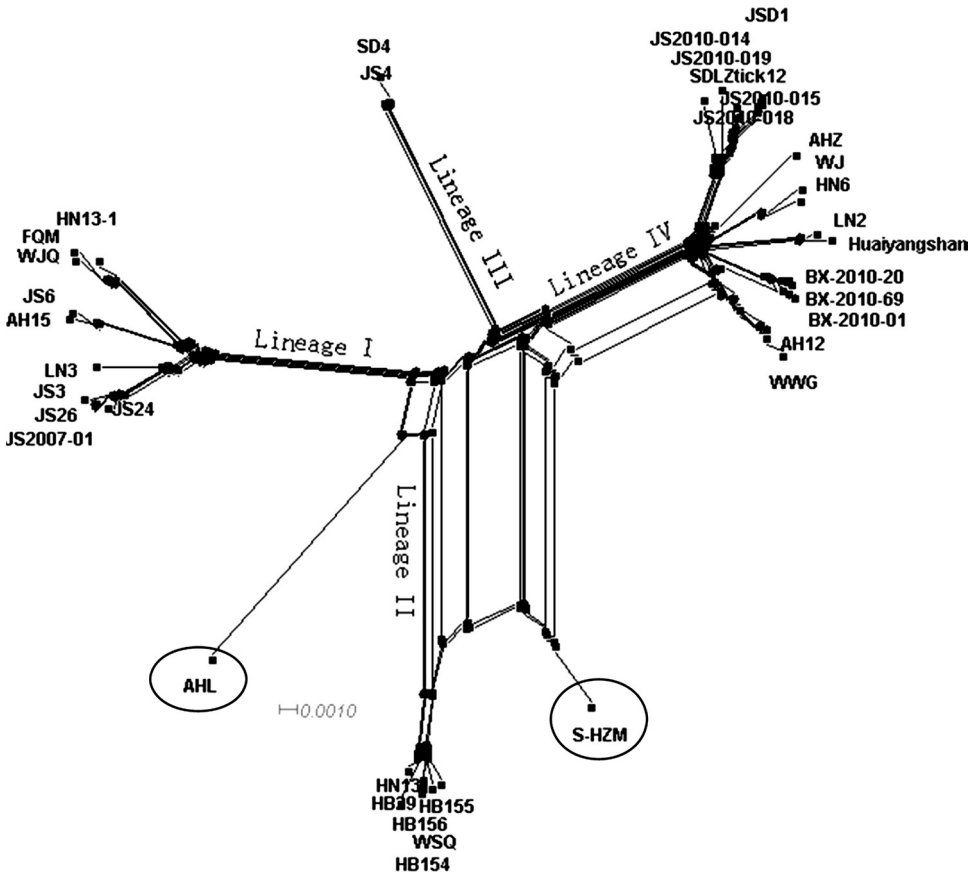

Fig. 1. The network evolutionary history of SFTSV circulating in China inferred from complete genome. The evolutionary relations were reconstructed using the Neighbor-Joining (NJ) method implemented in Splitstree 4.

SFTSV. According to the complete genome sequence, the split trees were constructed to identify phylogenetic network relation of these SFTSV isolates; and potential reassortment viruses were also sought for using recombination detection programs software package RDP2 (Martin et al., 2005). The genome sequence similarity were analyzed and displayed as graphics with Simplot software (Lole et al., 1999). At last, incongruent phylogenetic relations of different segments were used to determine the reassortment event based on ML, NJ, and MP phylogenetic trees.

According to the split tree of SFTSV complete genome sequences, these viruses can be divided into four individual lineages (Fig. 1). Two strains AHL and HZM had network evolution relations with lineages I and II, lineages II and IV, respectively. Phi test implemented in Splitstree (4.0) program provided a statistic significant recombination evidence ($p < 0.00001$). However, when the two strains were removed from the sequence alignment data, the recombination signal disappeared. These results suggested that both of them might have a mosaic genome. Using recombination analysis program RDP 2, the single recombination breakpoint was located at the 3′-end of S segment with statistical significance, suggesting that the two strains AHL and HZM were reassortants rather than intragenic recombinants.

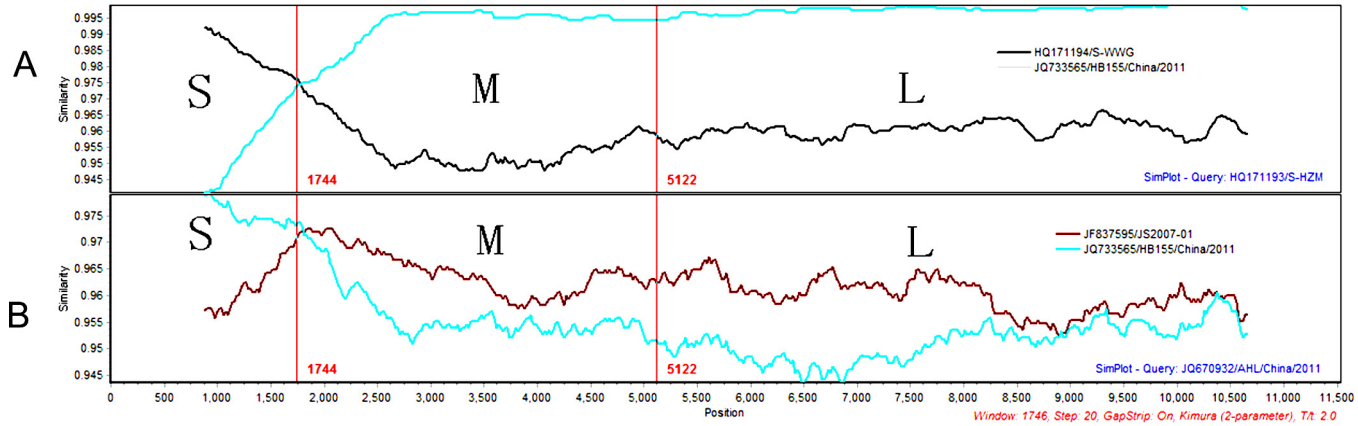

Fig. 2. A sequence comparison of the complete genome of the reassortment strains and their potential parental lineage representatives. Two strains HZM and AHL were respectively used as the query: (A) HZM; (B) AHL. The *y*-axis gives the percentage of identity within a sliding window 1744 bp wide centered on the position plotted, with a step size between plots of 20 bp. The red vertical lines represent the 3′-end of S segment (1744) and 5′ end of L segment of SFTSV. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)