CHAPTER 5

MOLECULAR EPIDEMIOLOGY, GENOMICS,
AND PHYLOGENY OF CRIMEAN-CONGO
HEMORRHAGIC FEVER VIRUS

ROGER HEWSON, PH.D.

Virus Research, Novel and Dangerous Pathogens, Centre for Emergency Preparedness and Response,
Health Protection Agency, Porton Down, Salisbury, SP4 0JG, England, UK.
Tel.: +44 (0)1980 612390; Fax: +44 (0)1980 610848; E-mail: Roger.Hewson@hpa.org.uk

5.1. INTRODUCTION

Crimean-Congo hemorrhagic fever virus (CCHFV) constitutes a group of viruses of the genus Nairovirus (family Bunyaviridae). Like all members of the Bunyaviridae, the genome of CCHFV is composed of tripartite single-stranded RNA. These segments, designated small (S), medium (M), and large (L), minimally encode the nucleocapsid (N), envelope glycoproteins (Gn and Gc), and RNA-dependent RNA polymerase (RdRp), respectively [38].

Published descriptions of major epidemics, outbreaks, and the ecology of CCHFV have been reviewed extensively [18, 43, 45]. Interestingly a common theme is illustrated by the very wide distribution of the virus, which stretches over much of Asia, extending from the Xinjiang region of China to the Middle East and southern Russia, and to focal endemic areas over much of Africa and parts of southeastern Europe. Thus, CCHFV is the most widely distributed agent of severe haemorrhagic fever known.

5.2. MOLECULAR EPIDEMIOLOGY

Classic serological methods have been important in determining CCHF distribution; however, these assays do not readily differentiate between alternative strains of CCHFV. In order to characterize viral strains in more detail and facilitate a global epidemiological study, molecular methods based on partial and complete sequence data of the S segment have been used to identify certain S segment genotypes [9, 13, 36]. These genotypes show a strong relationship to the geographical area of parent virus isolation, leading to the terminology Asia 1,
Asia 2, Europe 1, etc., which has been employed as a simple description of genotype (Fig. 5-1). Furthermore, these studies also show that similar genotypes are found in distant geographical locations (Fig. 5-2), supporting the idea that virus or infected ticks may be carried over long distances during bird migration [10]. Anthropogenic factors, such as the trade in livestock, may have also played a role in the dispersal of CCHFV. Thus, molecular epidemiological observations support a global and dynamic reservoir of CCHF virus.

Sequence information on L segments has lagged behind those of both S and M segments primarily due to the technical difficulties in working with these very long molecules. Nevertheless, several data from strains is available and while the number of alternative strains is on a different scale to those of S segments, there is evidence that the S and L segments from the same strains have similar evolutionary history (Fig. 5-3). For M segments however, the situation is different and it enables an insight into the ways CCHFV have evolved.

5.3. GENETIC VARIATION AND EVOLUTION

The driving force for evolution is provided by genetic change and variation in genomes. These lead to phenotypes which are molded by selective forces, thus genomes gradually change with their changing environments. RNA viruses, with their large population sizes, swift, and mutation-prone replication rates are generally considered capable of rapid evolution [16]. Additional evolutionary processes of (i) recombination, and for viruses with segmented genomes (ii) reassortment, also offer potentially important routes of generating genetic diversity. The genomes of arthropod-borne RNA viruses however, need to function and maintain high fitness in both arthropod and vertebrate host cells. This maintenance on two fronts is frequently thought to constrain the evolutionary processes acting on arbovirus genomes [44]. Thus, low levels of genetic diversity are frequently observed for arboviruses. The genome of CCHFV is interesting since, as well as showing features of high genetic stability [13], it also shows features of high flexibility [8]. CCHFV is often described as an emerging virus [22, 47]. Studies of its genetic fine structure aimed at developing a better understanding of the ways it can change and evolve are helping to illuminate its nature as an emerging pathogen. Complete genome entries of several CCHFV are now available in GenBank, and analysis of these sequences are enabling evolutionary hypothesis to be inferred and tested.

5.3.1. Recombination

Genetic homologous recombination – the formation of chimeric RNA molecules from sequences previously separated on different molecules – is an important means of variation open to RNA genomes. Indeed, it is clear that homologous recombination has been an important process that has shaped the evolution of RNA viruses per se [46]. However, the contribution of its effects