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Principal host relationships and evolutionary history of the North American arenaviruses

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Abstract

A previous study suggested that the genomes of the arenaviruses native to North America are a product of genetic recombination between New World arenaviruses with significantly different phylogenetic histories. The purpose of this study was to extend our knowledge of the principal host relationships and evolutionary history of the North American arenaviruses. The results of this study suggest that the large-eared woodrat (*Neotoma macrotis*) is a principal host of *Bear Canyon virus* and that the present-day association of *Bear Canyon virus* with the California mouse (*Peromyscus californicus*) in southern California represents a successful host-jumping event from the large-eared woodrat to the California mouse. Together, the results of analyses of viral gene sequence data in this study and our knowledge of the phylogeography of the rodents that serve as principal hosts of the New World arenaviruses suggest that genetic recombination between arenaviruses with significantly different phylogenetic histories did not play a role in the evolution of the North American arenaviruses.

Keywords: *Arenaviridae*; *Bear Canyon virus*; *Tamiami virus*; *Whitewater Arroyo virus*; Z protein; RNA-dependent RNA polymerase

Introduction

The virus family *Arenaviridae* comprises 2 serocomplexes and 22 species (Salvato et al., 2005). The Tacaribe (New World) complex includes *Bear Canyon virus* (BCNV), *Tamiami virus* (TAMV), and *Whitewater Arroyo virus* (WWAV) in North America, *Tacaribe virus* (TCRV) on Trinidad in the Caribbean Sea, and *Allpahuayo virus* (ALLV), *Amapari virus* (AMAV), *Cupixi virus* (CPXV), *Flexal virus* (FLEV), *Guanarito virus* (GTOV), *Junin virus* (JUNV), *Latino virus* (LATV), *Machupo virus* (MACV), *Oliveros virus* (OLVV), *Parana virus* (PARV), *Pichindé virus* (PICV), *Pirital virus* (PIRV), and *Sabiá virus* (SABV) in South America. The lymphocytic choriomeningitis–Lassa (Old World) complex includes *Ippy virus* (IPPYV), *Lassa virus* (LASV), *lymphocytic choriomeningitis virus* (LCMV), *Mobala virus* (MOBV), and *Mopeia virus* (MOPV).

Specific members of the subfamilies Neotominae and Sigmodontinae in the rodent family Cricetidae (Wilson and Reeder, 2005) are the principal hosts of the New World arenaviruses for which natural host relationships have been well characterized. For example, the hispid cotton rat (*Sigmodon hispidus*) in southern Florida is the principal host of TAMV (Calisher et al., 1970; Jennings et al., 1970), the white-throated woodrat (*Neotoma albigula*) in northwestern New Mexico is the principal host of WWAV (Fulhorst et al., 1996), and Alston's cotton rat (*Sigmodon alstoni*) in western Venezuela is the principal host of PIRV (Fulhorst et al., 1997, 1999).

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The California mouse (*Peromyscus californicus*) is a natural host and may be a principal host of BCNV (Fulhorst et al., 2002). Bear Canyon is located in the Santa Ana Mountains in western Riverside County near the Riverside County–Orange County line. The BCNV prototype strain AV A0070039 was isolated from a California mouse captured in November 1998 in Riverside County near Bear Canyon (Fulhorst et al., 2002). Strains of BCNV subsequently were isolated from 4 (19.1%) of 21 California mice captured in June 1998 at 2 sites in the Santa Ana Mountains in eastern Orange County (Fulhorst et al., 2002).

In previous studies (Bennett et al., 2000; Fulhorst et al., 2002), antibody to an arenavirus was found in 1 (50.0%) of 2 dusky-footed woodrats (*Neotoma fuscipes*) and 4 (50.0%) of 8 California mice captured in western Riverside County near Bear Canyon, 5 (16.1%) of 31 dusky-footed woodrats and 7 (21.9%) of 32 California mice captured at 7 sites in eastern Orange County, and 3 (6.8%) of 44 dusky-footed woodrats and 1 (4.2%) of 24 California mice captured at 14 sites in southern Orange County. Note that the large-eared woodrat (*Neotoma macrotis*) in Riverside County, Orange County, Los Angeles County, and other counties in southern California recently was elevated from subspecific status within the *N. fuscipes* species complex (Matocq, 2002). Thus, the antibody-positive woodrats captured in Riverside County and in Orange County in the previous studies likely were large-eared woodrats, not dusky-footed woodrats.

Studies done in the 1990s established that multiple (different) arenaviruses coexist in certain regions of South America. For example, JUNV and OLVV are sympatric in the pampas of northern Argentina (Mills et al., 1996) and GTOV and PIRV are sympatric on the plains of western Venezuela (Fulhorst et al., 1997, 1999). Hypothetically, BCNV is not the arenavirus associated with the large-eared woodrat in the Santa Ana Mountains. The first objective of the present study was to determine the identity of the arenavirus associated with the large-eared woodrat in southern California.

Arenaviruses possess genomes that consist of 2 single-stranded RNA segments, designated small (S) and large (L) (Southern, 1996). The S segment (~3.5 kb) consists of a 5′ noncoding region (NCR), the glycoprotein precursor (GPC) gene, an intergenic region that separates the GPC gene from the nucleocapsid (N) protein gene, the N protein gene, and a 3′ NCR. Similarly, the L segment (~7.3 kb) consists of a 5′ NCR, the Z gene, an intergenic region that separates the Z gene from the RNA-dependent RNA polymerase (RdRp) gene, the RdRp gene, and a 3′ NCR.

Independent analyses of complete GPC sequences and complete N protein sequences in a previous study (Charrel et al., 2002) delineated 5 phylogenetic lineages within the *Arenaviridae*: North American (BCNV, TAMV, and WWAV), South American lineage A (ALLV, FLEV, PARV, PICV, and PIRV), South American lineage B (AMAV, CPXV, GTOV, JUNV, MACV, SABV, and TCRV), South American lineage C (LATV and OLVV), and Old World (LASV, LCMV and MOPV). Note that the analysis of the GPC sequence data placed the North American lineage in a sister relationship to the South American lineage B whereas the analysis of the N protein sequence data placed the North American lineage in a sister relationship to the South American lineage A. Also note that the monophyly of the North American lineage and the South American lineage B in the analysis of the GPC sequence data and the monophyly of the North American lineage and the South American lineage A in the analysis of the N protein sequence data were strongly supported by the results of bootstrap analyses (Felsenstein, 1985).

Previously, our most comprehensive knowledge of the evolutionary history of the arenaviral L genomic segment was based on analyses of amino acid sequences predicted from a small fragment (288- to 300-nt) of the RdRp genes of BCNV strain AV A0060209, TAMV strain W-10777, WWAV strain AV 9310135, TCRV strain TRVL II573, 11 South American arenaviruses, and 3 Old World arenaviruses (Charrel et al., 2003). In a neighbor-joining analysis of the RdRp sequence data, the 3 North American arenaviruses were monophyletic, the North American lineage was sister to a lineage that comprised ALLV, PICV and PIRV, and the BCNV–TAMV–WWAV–ALLV–PICV–PIRV lineage was sister to a lineage that comprised AMAV, CPXV, GTOV, JUNV, MACV, SABV and TCRV. Thus, the L segments (RdRp genes) and the 3′ halves of the S segments (N protein genes) of the North American arenaviruses appear to be descended from an ancestor of the South American lineage A viruses that emerged after the divergence of the South American lineage A from the South American lineage B. The second objective of this study was to extend and refine our knowledge of the phylogenetic history of the North American arenaviruses, specifically to determine whether the L genomic segments of BCNV, TAMV, and WWAV are a product of homologous recombination between the L segment of a South American lineage A virus and the L segment of a South American lineage B virus.

Results

Strain AV 98470029 is an arenavirus that was isolated in this study from a large-eared woodrat captured in September 1998 in the Santa Ana Mountains in Riverside County. The BCNV strains AV A0060209 and AV A0070039 were isolated in a previous study (Fulhorst et al., 2002) from California mice captured in the Santa Ana Mountains in Orange County and Riverside County, respectively. The nucleotide sequences of the GPC and N protein genes of AV 98470029 were compared to the homologous sequences of AV A0060209, AV A00 70039, TAMV strain W-10777, WWAV strain AV 9310135, TCRV strain TRVL II573, and 7 South American arenaviruses (Table 1). In pairwise comparisons, the nucleotide sequence of the GPC gene of AV 98470029 was 97.0%, 98.1%, 64.0%, and 62.5% identical to the nucleotide sequences of the GPC genes of BCNV strain AV A0060209, BCNV strain AV A00 70039, TAMV strain W-10777, and WWAV strain AV 931 0135, respectively, and less than 57.3% identical to the nucleotide sequences of the GPC genes of TCRV strain TRVL II573 and the 7 South American arenaviruses included in this study (Table 2). Similarly, the nucleotide sequence of the N