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Genome Sequence of Erythromelalgia-Related Poxvirus Identifies it as an Ectromelia Virus Strain

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Abstract

Erythromelalgia is a condition characterized by attacks of burning pain and inflammation in the extremeties. An epidemic form of this syndrome occurs in secondary students in rural China and a virus referred to as erythromelalgia-associated poxvirus (ERPV) was reported to have been recovered from throat swabs in 1987. Studies performed at the time suggested that ERPV belongs to the orthopoxvirus genus and has similarities with ectromelia virus, the causative agent of mousepox. We have determined the complete genome sequence of ERPV and demonstrated that it has 99.8% identity to the Naval strain of ectromelia virus and a slighly lower identity to the Moscow strain. Small DNA deletions in the Naval genome that are absent from ERPV may suggest that the sequenced strain of Naval was not the immediate progenitor of ERPV.

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Introduction

Erythromelalgia is a condition in which there are attacks of burning pain and inflammation in the extremities. Primary hereditary erythromelalgia is a rare disease caused by a mutation in a voltage-gated sodium channel subunit [1,2]. Non-hereditary erythromelalgia has an incidence of approximately 1.3 per 100,000, occurring most frequently in women with a median age of 61, and can have multiple causes [3]. In rural China, outbreaks of erythromelalgia have occurred during the winter and spring at several year intervals among secondary school students [4–8]. In a 1987 epidemic, many students reported pharyngitis prior to the symptoms of erythromelalgia suggesting a possible connection with a respiratory tract infection [9]. Virus isolates from throat swabs of six individuals in three locations suffering from erythromelalgia were characterized [4,10]. In five cases the virus was isolated directly in cell culture and in another was first passaged in mice [11]. In addition, the sera from patients with epidemic erythromelalgia were reported to have a higher incidence of ERPV antibody (39.2%) compared to non-symptomatic local students (11.8%) and sera of controls from the United States (11.9%) [12]. Electron microscopic examinations indicated that the isolated virus belongs to the poxvirus family [13]. Further analysis of the biological, serological and pathogenic properties suggested that erythromelalgia-related poxvirus (ERPV) is a member of the orthopoxvirus genus [11]. A restriction enzyme profile of the ERPV DNA resembled but was distinguishable from a Chinese strain of ectromelia virus (ECTV), the causative agent of mousepox [14]. The susceptibility of mice to ERPV and the formation of A-type inclusion bodies in the cytoplasm were also consistent with ECTV. However, there were apparent differences between the Chinese strain of ECTV and ERPV with regard to pock morphology on the chicken chorioallantoic membrane, pathogenicity for rabbits, and the ability of ERPV to be neutralized by anti-vaccinia virus and anti-ECTV sera from rabbits but not vice-versa [11]. Moreover, ECTV is not known to cause disease in humans. In contrast, human infections are known to occur with other orthopoxviruses including variola virus (smallpox), cowpox virus, monkeypox virus and vaccinia virus [15].

Poxviruses are large double-stranded DNA viruses [16]. The availability of Next Generation sequencing technologies allowed us to sequence and analyze the genome of ERPV. We compared the ERPV genome sequence to that of the complete genome sequences of the Moscow (ECTV-Mos) [17] and Naval (ECTV-Nav) [18] (www.poxvirus.org) strains of ECTV and determined that it closely resembled the latter with only minor differences.

Results

Sequence of the ERPV Genome

The genomes of orthopoxviruses are approximately 200,000 base pairs (bp) with two long inverted terminal repetitions (ITRs); within each ITR there are usually a few open reading frames (ORFs), sets of short direct repeats (DRs), a unique concatemer resolution sequence (CRS), and a terminal covalently closed hairpin loop (Fig. 1). ERPV was obtained from the American Type Culture Collection, clonally purified and ampli-