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Phylogenetic and Evolutionary Studies of Flavivirus

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Abstract:**Viruses of Flavivirus genus are the causative agents of many common and devastating diseases, including yellow fever, dengue fever etc. so for proper development of efficient anti viral pharmaceutical strategies there is a need for proper classification of viruses of this group. To generate the most diverse phylogenetic datasets for the Flaviviruses to date, we analyzed the whole genomic sequences and phylogenetic relationships of 44 Flaviviruses by using various bioinformatics tools (MEGA, Clustal W, and PHYLIP). We analyze these data for understanding the evolutionary relationship between classified and unclassified viruses and to propose for the reclassification of unclassified viruses which shows sequence similarity and also similar mode of transmission with classified viruses.

Key words: Viruses, Flavivirus, Phylogenetic.

1. INTRODUCTION

Viruses of the Flaviviridae family infect vertebrates and they are primarily transmitted through arthropod vectors (mainly ticks and mosquitoes) [1]. The Flaviviruses constitute a fascinating group of diverse arboviruses that exhibit uniquely clear correlations between phylogenetic relationships and virus-vector-host interactions [2]. Flaviviridae are enveloped, positive single-stranded RNA viruses [3]. The Flaviviridae family includes four genera: Flaviviruses (Yellow fever virus, West Nile virus, Dengue virus, Tick-borne encephalitis viruses), Hepacivirus (Hepatitis C virus), Pestivirus (Classical swine fever virus, Bovine viral diarrhea virus) and Unclassified Flaviviridae (Hepatitis GB virus, GB viruses) [4]. The genus Flavivirus of the family Flaviviridae comprises over 70 viruses, many of which, such as the dengue (DEN) viruses, Japanese encephalitis (JE) virus, St. Louis encephalitis (SLE) virus, and yellow fever (YF) virus are important human pathogens [5]. Flaviviruses may be (i) arthropod-borne, infecting a range of vertebrate hosts through mosquito or tick bites, (ii) presumed to be limited to vertebrates alone or (iii) apparently limited to insects alone. The last group, referred to as the ‘insect-specific’ Flaviviruses, contains tentative members of the genus Flavivirus that appear to replicate only in mosquito cells and not in mammalian cells figure (1) [6].

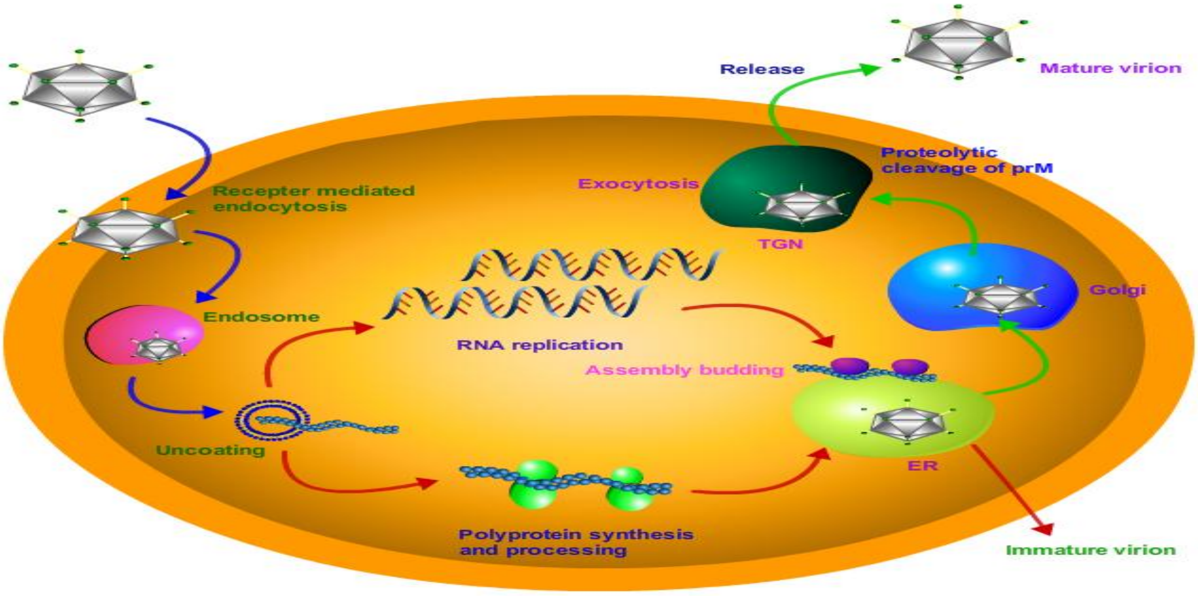

Figure 1: Life cycle of Flaviviridae virus. The figure was made with tools from www.proteinlounge.com

Pathogenic mosquito- and/or tick-borne Flaviviruses cause a variety of clinical diseases in a wide range of vertebrate species. These disease syndromes include mild/severe febrile illness, “flu-like” syndromes with a rash, or in other cases severe encephalitis or haemorrhagic disease [7]. Flaviviridae have monopartite, linear, single-stranded, positive sense RNA genomes [8]. Ranging from 10 to 12.5 kilo bases (kb) in length [9]. Virions of the Flaviviridae family are enveloped and slightly pleomorphic during their life cycle. They are spherical in shape and usually 40–60 nm in diameter. Their nucleocapsids are isometric and sometimes penetrated by stain. The usual size of the nucleocapsids is 25–30 nm in diameter and they have polyhedral symmetry [10]. The concept that the phylogenetic relationships of the tick-borne Flaviviruses (TBFV) may correlate with their epidemiology, disease association and biogeography was first proposed in 1996 with the publication of the clinical evolution concept of the tick-borne encephalitic Flaviviruses [11]

II MATERIALS AND METHODS

Data collection is an important aspect of any type of research study. Accurate data collection is essential to maintain the integrity of research. So for the purpose of comparative genome analysis of viruses of Flavivirus data needs to be collected which contains the reference sequences. The sequences of 44 viruses of Flavivirus genus are retrieved in this study whose reference sequences had been already available on NCBI (National Center of Biotechnology Information). These sequences include 44 sequences from the Flavivirus. The multiple sequence alignment programs Clustal W offline [12] was used to obtain an optimal nucleotide or amino acid sequence alignment file. Phylograms for the entire sequence were obtained either by MEGA version 5.10 [13] or by PHYLIP version 3.6 [14] based on aligned nucleotide or amino acid sequences.

For tree building various genetic distance matrices were used for the neighbor joining method which calculated bootstrap confidence intervals of 500.We also tested a character state tree building algorithm which consisted of a sequential programs in the PHYLIP package. A strict consensus bootstrap tree was obtained by using the following programs:

(1) SEQBOOT to generate reiterated replicas
(2) DNAPARS to acquire the most parsimony tree of each reiterated data
(3) CONSENSE to build a strict consensus boot strap tree
(4) DRAWGRAM to draw the phylogenetic tree.

Table1: Flaviviruses used in phylogenetic studies

Flaviviruses	**Distribution**	**Reference no.**
Murray Valley encephalitis	Australia, Papua New Guinea	NC_000943.1
Usutu virus	Africa	NC_006551.1
Japanese encephalitis virus	Asia and parts of the pacific	NC_001437.1
West Nile virus	Africa, Asia, Europe	NC_009942.1
West Nile virus	Africa, Asia, Europe	NC_001563.2
St. Louis encephalitis virus	Americas	NC_007580.2
Ilheus virus	Central and South America, Trinidad	NC_009028.2
Tembusu virus	Southeast Asia	NC_015843.2
Bagaza virus	Central African Republic	NC_012534.1
Ntaya virus	Central and South Africa	NC_018705.3
Bussuquara virus	South America	NC_009026.2
Kokobera virus	Australia	NC_009029.2
Kedougou virus	Senegal	NC_012533.1
Zika virus	Africa, Asia	NC_012532.1
Dengue type 4 virus	Tropical and semitropical areas	NC_002640.1
Dengue type 2 virus	Thailand	NC_001474
Dengue type 1 virus	Tropical and semitropical areas	NC_001477.1
Dengue type 3 virus	Tropical and semitropical areas	NC_001475.2
Chaoyang virus	Republic of korea	NC_017086.1
Donggang virus	CHINA	NC_016997.1
Yokose virus	Japan	NC_005039.1
Entebbe bat virus	Uganda	NC_008718.1
Yellow fever	Tropical areas	NC_002031.1
Sepik virus	Papua New Guinea	NC_008719.1
Wesselsbron virus	South Africa	NC_012735.1
Montanamyotis leukoencepalitis virus	Montana	NC_004119.1
Rio Bravo virus	United States, Mexico	NC_003675.1
Modoc virus	Western United States	NC_003635.1
Apoi virus	Japan	NC_003676.1
Tyuleniy virus	Russia, Oregon	NC_023424.1
Kama virus	Russia, kanya	NC_023439.1
Karshi virus	Kazakhstan	NC_006947.1
Powassan virus	North America, Russia	NC_003687.1
Alkhumra virus	Saudi Arabia	NC_004355.1
Langat virus	Southeast Asia, Russia	NC_003690.1
Omsk hemorrhagic fever virus	Russia, Siberia	NC_005062.1
Louping ill virus	Siberia and the UK	NC_001809.1
Tick-borne encephalitis virus	Europe	NC_001672.1
Aedes Flavivirus	Kenya	NC_012932.1
Kamiti River virus	USA	NC_005064.1
Cell fusing agent virus	Unknown	NC_001564.1
Culex Flavivirus	Japan	NC_008604.2
Mosquito Flavivirus	China	NC_021069.1
Quang Binh virus	Vietnam	NC_012671

III RESULTS AND DISCUSSION

The phylogenetic tree figure (2) was constructed by the neighbor-joining method of MEGA for nucleotide sequences. Each number at nodes is the percentage of 1000 bootstrap replicate support. According to phylogenetic tree the whole genus is divided into two groups vector borne and non vector borne. The phylogram reveals that non-vector and vector-borne clusters emerged first from the putative origin of the genus Flavivirus. The latter further branched off to form tick-borne and mosquito-borne virus clusters [15]. These three clusters are well supported by 99% of bootstrap replicates. The non-vector cluster further branched into Montana myotis leukoencephalitis, Riobravo virus, Modoc, Apoi. Mosquito borne viruses can be further divided into mosquito borne culex, Mosquito borne ades. Yellow fever virus group comes under Mosquito borne ades. The viruses belongs to arthropod specific group has mosquito as their vector these all viruses belongs to unclassified Flaviviruses. The Tick-borne encephalitis virus groups include total number of nine viruses Tyuleniy, Kama, Karshi, Powassan, Alkhumra, Langat, Omsk Hemorrhagic fever, Louping ill. The mode of transmission of Tick borne encephalitis viruses is through tick. Murray valley encephalitis(MVE), Usutu, Japanese encephalitis, Westnile, St. Louis encephalitis, Ilehus, Tembusu, Bagaza, Nataya, Bussuquara, kokobera these viruses are more closely related with high bootstrap value and they have same mode of transmission by a Culex Mosquito. Dengue 1-4, zika, Kedoungo, chaoyang, donggang these all viruses are Mosquito borne ades viruses and they also have some mode of transmission. This group contains two unclassified Flavivirus chaoyang, donggang and these both viruses share sequence similarity with other viruses of this group. Since some viruses belonging to the unclassified Flavivirus group show similarity and phylogenetic relationship with classified viruses group and their mode of transmission is also same. Aedes Flavivirus, Cell fusing agent virus, chaoyang virus, Culex Flavivirus, donggang virus, Kamiti River virus, Mosquito Flavivirus, Quang Binh virus show similarity with mosquito borne viruses and kama virus with tick borne viruses. So on the basis of phylogenetic relationship shown by unclassified viruses with other grouped viruses and also on the basis of same mode of transmission we can propose for the reclassification of unclassified flaviviruses.

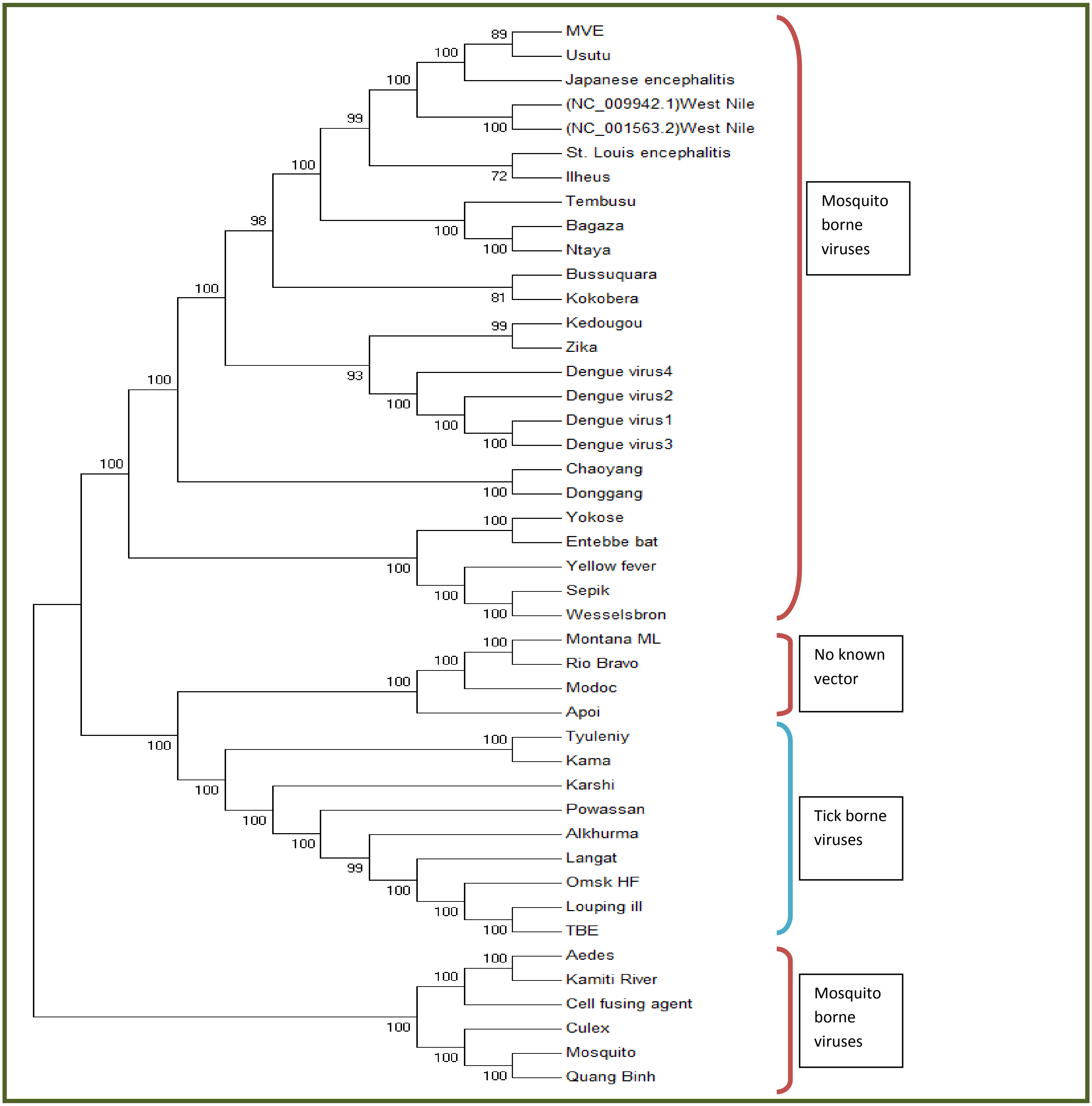

Figure 2: Phylogenetic tree of Flavivirus using amino acid sequence constructed by MEGA.

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