Genetic Elements Involved in Zika Virus Neuropathogenesis

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Introduction

Zika virus (ZIKV) is a mosquito-borne flavivirus (**Fig. 1**) that is closely related to Japanese encephalitis, West Nile, yellow fever, and dengue viruses. ZIKV was first discovered in Uganda in 1947, but it was not until recent outbreaks, such as through Micronesia in 2007 and through Brazil in 2015 (**Fig. 2**), that it has been found to be associated with neurological diseases such as Guillain-Barré syndrome and microcephaly.

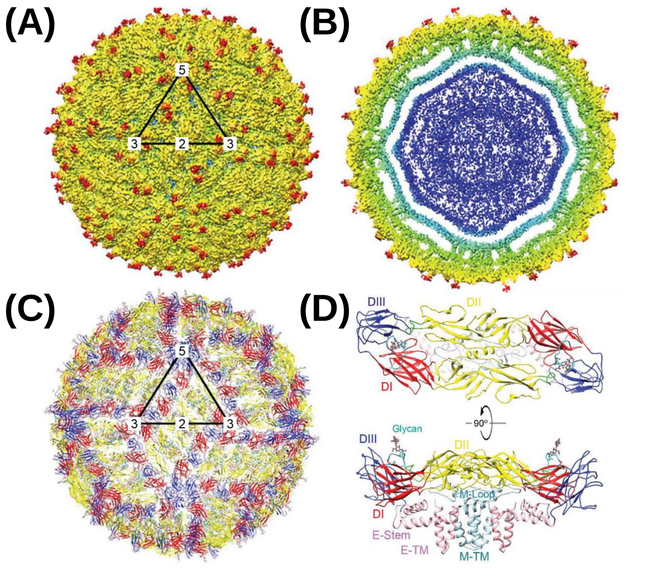


Fig 1. (***A***) A surface-shaded and depth-cued representation of ZIKV. (***B***) A cross-section of ZIKV showing the radial density distribution. (***C***) The Cα backbone of the E and M proteins in the icosahedral ZIKV particle. (***D***) The E protein dimer and E-M dimer in ribbon form with labeled domain I (red), domain II (yellow), domain III (blue), the M loop and stem/transmembrane domain (light blue), and E stem/transmembrane domain (pink).

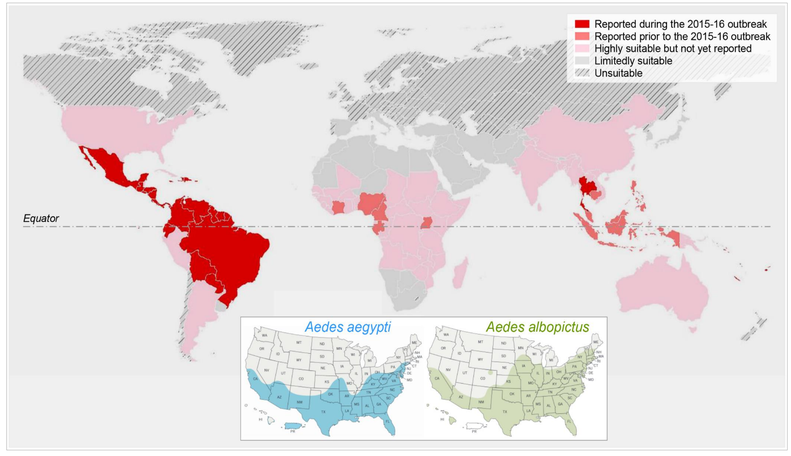


Fig 2. Global reporting of ZIKV accompanied by regions with suitable climate for further transmission.

ZIKV can be divided into two major genetic lineages, African and Asian, with the 2015-2016 American epidemic strains derived from a common ancestor of the Asian lineage (**Fig. 3**). Comparing the neuro-pathogenesis in mice of these strains reveals that the African strain MR-766 is highly virulent, the American strain PRVABC-59 is essentially avirulent, and the Asian strain P6-740 shows an intermediate phenotype. In this study, we have used ZIKV P6-740 as a parental virus to understand the viral genetic elements involved in ZIKV neuropathogenesis.

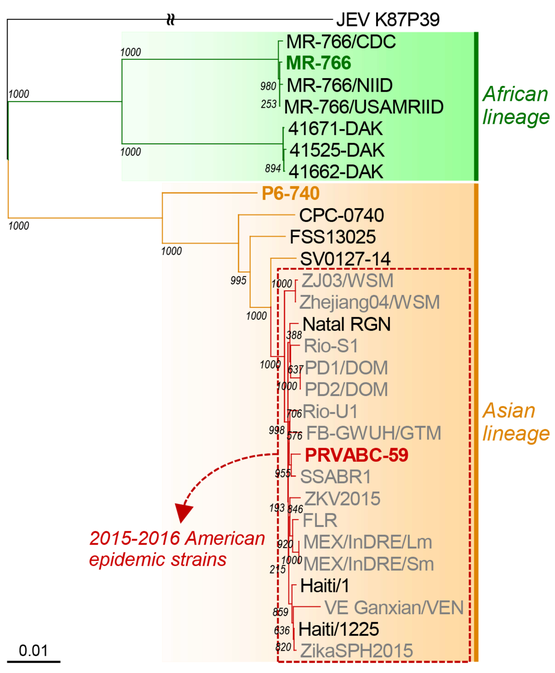
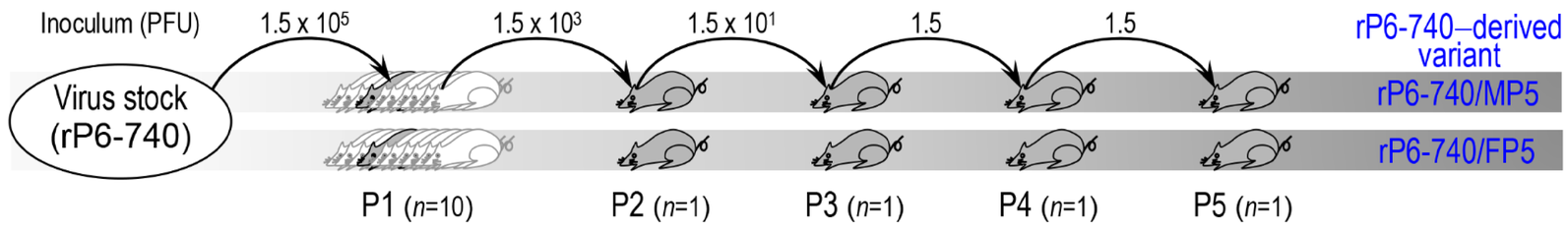


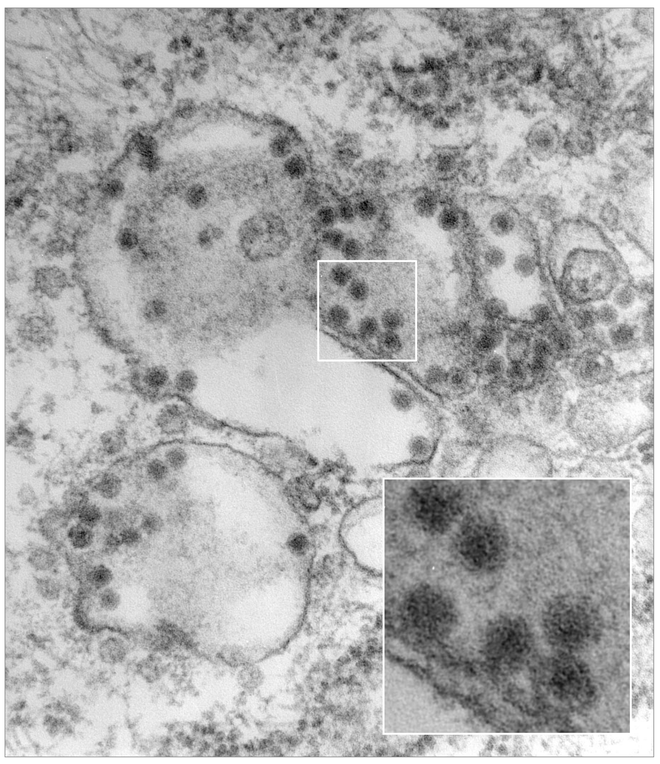
Fig 3. The phylogenetic tree of ZIKV. Highlighted are the two genetic lineages, African (green) and Asian (orange), together with the eighteen 2015-2016 Latin American epidemic strains (red) that belong to the Asian lineage.

Methods

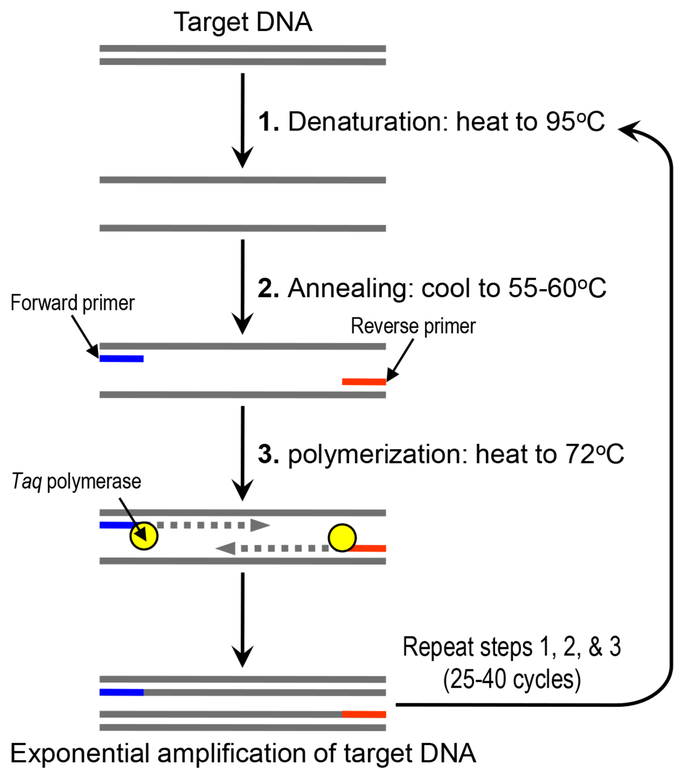
1. Serial passage in mice



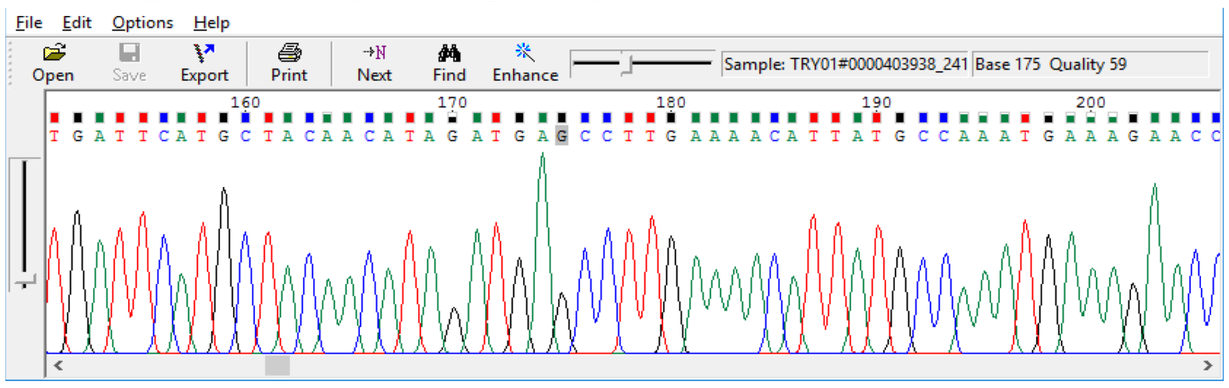
2. Virus isolation



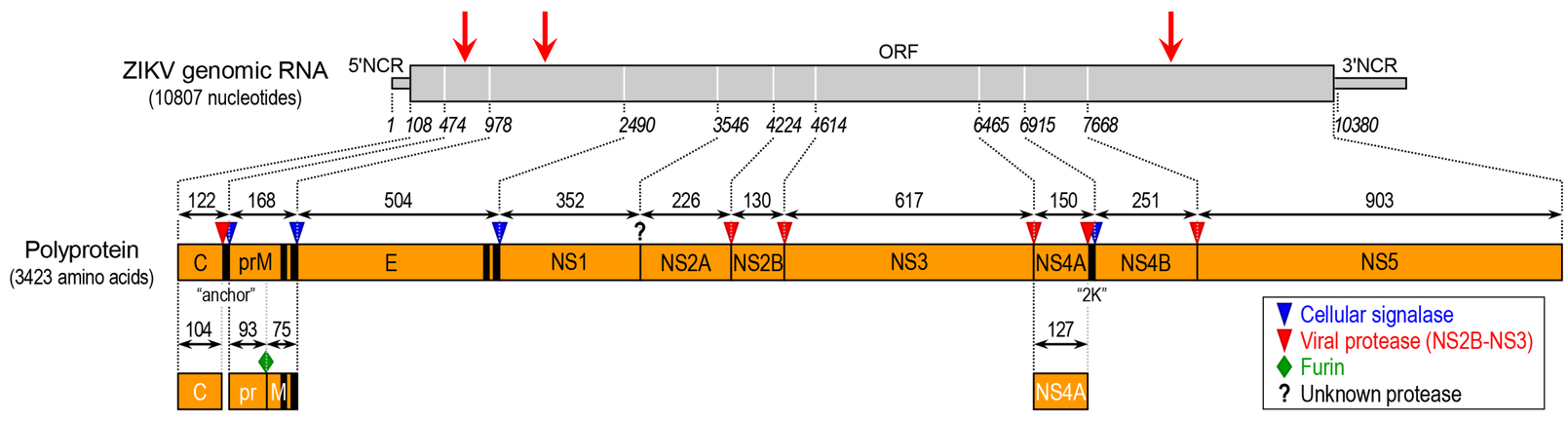
3. Three overlapping cDNA synthesis



4. Whole genome sequencing analysis



Results and Conclusion



We are in the process of whole-genome sequencing. Thus far, we found three point mutations, each in prM, E, and NS5 protein coding region, suggesting that one or more of these genetic changes in the viral genome affects ZIKV neuropathogenesis. Further studies will be conducted to identify the genetic elements that are responsible for ZIKV neuropathogenesis.

References

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Acknowledgments

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