Elsevier has created a Monkeypox Information Center in response to the declared public health emergency of international concern, with free information in English on the monkeypox virus. The Monkeypox Information Center is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

A distinct phylogenetic cluster of Monkeypox genomes suggests an early and cryptic spread of the virus

To the Editor

Orviz et al. recently described the outbreak of monkeypox in Spain, which is part of a larger European outbreak, in this journal.[1] The outbreak has been epidemiologically linked to potential superspreader events in Europe earlier in the year 2022 and over a short period has spread across 75 countries causing over 20,000 infections as on 30 July 2022, with the World Health Organization subsequently declaring the outbreak as a public health emergency of international concern in July 2022.[2] Following the outbreak, the wide availability of monkeypox genome sequences in the public domain provided a unique opportunity to understand the genetic epidemiology as well as the evolution of the pathogen.

With heightened surveillance and molecular diagnosis across the globe, several genomes of the monkeypox virus are being deposited in public databases like GISAID.[3] As early epidemiologic studies linked the outbreak of monkeypox in 2022 to superspreader event(s) in Europe, it was therefore not surprising that a majority of the genomes available on GISAID cluster together (clade IIb). Further reports suggest that the early transmission in this outbreak was largely amongst gays, bisexuals and other men who have sex with men (MSM) with some exceptions.[4,5] However, the recently deposited genome sequences from the United States of America, Thailand and much more recently from India suggest a distinctly different phylogenetic cluster of genomes within clade IIb, classified by Nextclade as lineage A.2, in contrast to the cluster encompassing the majority of genomes ($N = 547$) that are classified as lineage B.1 (Fig. 1A).[6,10,11] The A.2 lineage comprises 9 genomes from 6 unique clinical isolates, with the earliest genome belonging to this lineage (collected in July 2021) being deposited from the state of Texas, USA. The two genome isolates from India cluster closely with a genome isolate from Florida (hMpxV/USA/FL-DHCPPCDC-001/2022) on the phylogenetic tree, while the isolates from Texas, Virginia and Thailand mapped to separate sub-clusters (Fig. 1B).

The genomes belonging to the A.2 lineage have 16 distinct genetic variations which are not found in other lineages, of which 9 are nonsynonymous, 3 are synonymous and 1 is a stopgain variation, along with a deletion of 3-amino acid deletion in the gene OPG174 (Fig. 1C). Variants found at a minimum frequency of 90% in the respective lineages A.2 and B.1 were compared and are summarised in Fig. 1C.

Albeit the limited number of sequences available for the A.2 lineage, we attempted to compute the time to the most recent common ancestor (tMRCA) for A.2 and the nucleotide substitution rates for lineages A.2 and B.1 using BEAST v1.10.4.[7] The tMRCA was calculated following a coalescent growth rate model with a strict molecular clock and the HKY+Γ substitution model. MCMC was run for 50 million steps and the initial 1% steps were discarded as burn-in. The tMRCA of the A.2 lineage was computed as 25 June 2021 (95% HPD 19 March 2021 to 1 July 2021). The A.2 lineage had a mean nucleotide substitution rate of 5.53×10^{-5} (95% HPD 3.39×10^{-5} to 7.46×10^{-5}) substitutions per base/year, suggesting a modest rate of substitution compared to the substitution rate of 1.13×10^{-4} (95% HPD 9.33×10^{-5} to 1.33×10^{-4}) substitutions per base/year for the larger B.1 lineage of genomes. Accelerated evolution of the B.1 lineage has been observed recently.[8]

Limited demographic information could be linked to the members of the A.2 cluster and has been primarily compiled from the metadata associated with the genome sequences as well as reports in the public domain. The two genomes from Kerala, India were isolated from men who had a travel history to the United Arab Emirates, while the genome from Thailand was isolated from a male traveller from Nigeria. The genome from Texas, United States of America, the earliest in the cluster, was also isolated from a male traveller from Nigeria suggesting a wider geographic area with ongoing transmission of the virus beyond regions in Central and Eastern Africa where the virus is endemic.[9]

Put together, the evidence suggests that this unique and distinct phylogenetic cluster of genomes, therefore, represents sustained and previously uncharacterized human-human transmission events spanning multiple countries. The tMRCA dating to mid-2021 and the earliest genome dating to July 2021 suggests that this sustained transmission event possibly preceded the outbreak in 2022 in Europe and has remained largely undetected. The distinct genomic signatures suggest that this transmission chain may not be linked to the large outbreak of monkeypox which occurred in 2022 and has been potentially uncovered due to heightened awareness, surveillance and the wider availability of diagnostics.

This report, therefore, re-affirms the unique and significant value of genomic surveillance of emerging pathogens in uncovering potential new insights and leads for epidemiological investigations. The distinctive finding in this report may have a significant impact on public health policies, surveillance as well as public-health communication.

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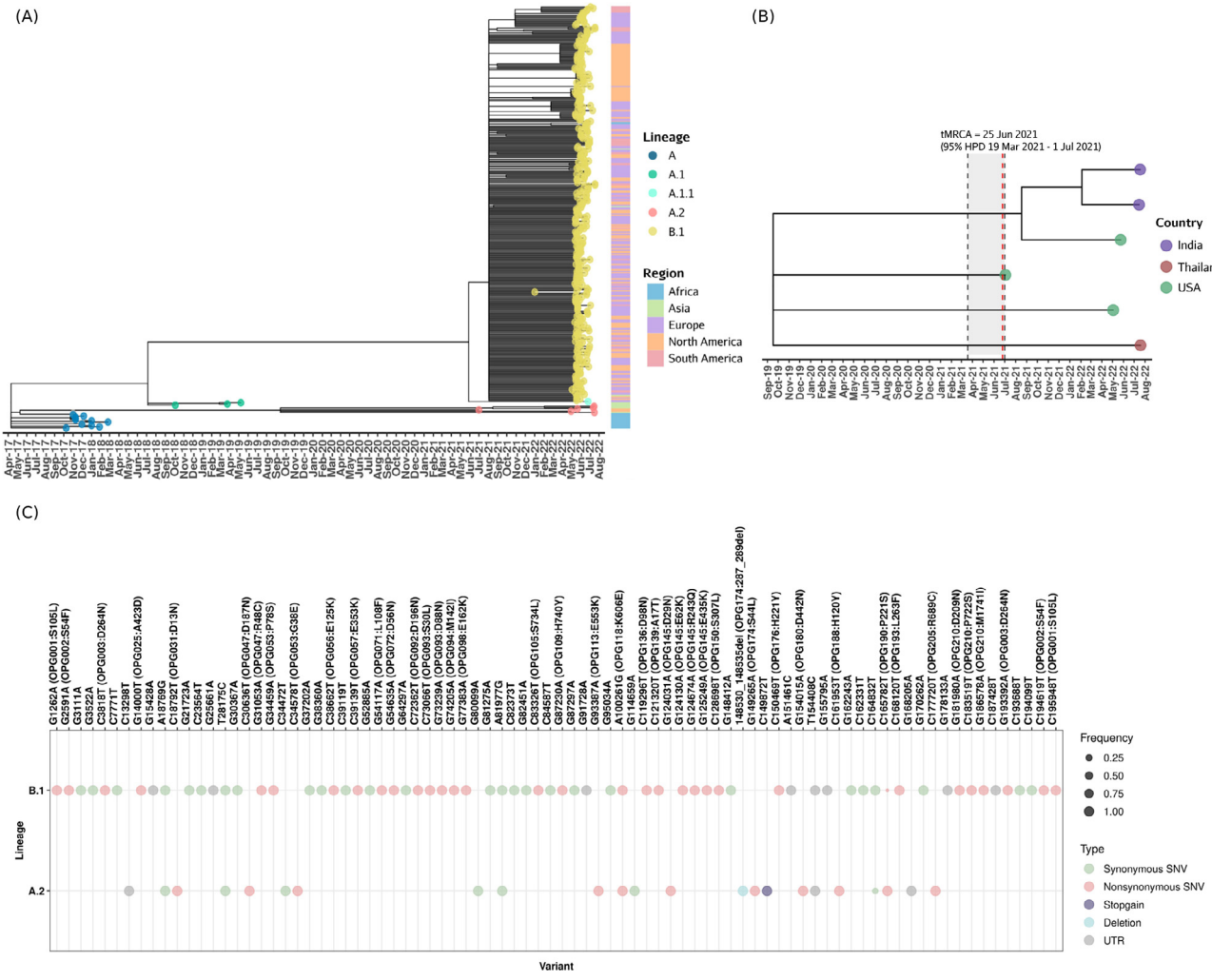

Fig. 1. (A) Phylogenetic tree of genome isolates from GISAID belonging to the hMPXV-1 clade of monkeypox virus constructed using Nextstrain.[6] (B) Phylogenetic tree of the genomes belonging to A.2 monkeypox lineage. (C) Comparison of frequencies of variations present in >90% genomes of lineages A.2 ($N = 6$) and B.1 ($N = 547$).

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Declaration of Competing Interest

The authors report no potential conflicts of interest.

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Bani Jolly, Vinod Scaria*
CSIR Institute of Genomics and Integrative Biology (CSIR-IGIB), Mathura Road, New Delhi, India
Academy for Scientific and Innovative Research, Human Resource Development Centre Campus, Ghaziabad, Uttar Pradesh, India

*Corresponding author at: G. N. Ramachandran Knowledge Centre for Genome Informatics, CSIR-Institute of Genomics and Integrative Biology, Sukhdev Vihar, New Delhi 110025, India.
E-mail address: vinods@igib.in (V. Scaria)