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Original

Human monkeypox: Will its evolutionary genetics lead us to a new pandemic?

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Human monkeypox is a disease caused by an Orthopoxvirus with signs and symptoms like those of smallpox. The disease is endemic in the Democratic Republic of the Congo and was diagnosed in 1970; since then, outbreaks have been reported mainly in rural areas of the Congo Basin and West Africa (1). However, in recent years it has spread to other regions of Africa and new cases have emerged in other continents, alerting health systems to a possible health emergency (2).

The current epidemiological context poses a certain degree of uncertainty to researchers regarding the dynamics of viral transmission and the magnitude of this outbreak. The natural reservoir of human monkeypox virus (MPX) is unknown; although rodents and non-human primates can carry the virus and could lead to occasional zoonotic events (3). MPX can be transmitted from human to human by close contact with lesions, bodily fluids, nasal discharge droplets, and contaminated materials.

The number of MPX cases has increased by at least 10 times compared to the first outbreak and has mainly affected young adults (2). The affectation of this age group could be related to the cessation of vaccination against smallpox, which provides cross immunity in around 85% against MPX (2). That is, the discontinuation of general vaccination beginning in the 1980s has resulted in increased susceptibility to MPX infection in humans; situation that has facilitated the generation of new shoots. The reactivation of the vaccination against the human smallpox virus would generate herd immunity, and therefore, a decrease in the spread of MPX would be expected (4).

In addition to immunity, another concern and possible reason for the resurgence in MPX cases is deforestation, which produces greater interactions between the human population and wild animals (5). However, the genetic evolution of MPX has now become the main topic of discussion. Comparative genome studies have shown that the evolution of Orthopoxviruses was driven by selective pressure from a host species (6). Additionally, it has been postulated that the progressive loss of genes, mainly at the terminal ends of the genome, has been the main factor in evolution (3,6). This has originated the A.2 and B.1 lineages, which circulate and have initiated different outbreaks in Asia and Europe (3,6)

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In 2014, an analysis of the genomic diversity of the virus in 60 human samples obtained from primary and secondary cases of infection in the Sankuru district, Democratic Republic of the Congo (6), revealed four lineages within the Central African clade. The analysis revealed a loss of 17% of the genes in the samples that seemed to correlate with person-to-person transmission. This supports a possible combination of destabilization and genetic polymorphism that influenced the MPXV strains circulating in the Sankuru district. In addition, predictive models of Orthopoxvirus genomic evolution were consistent with patterns of gene destabilization and loss (6,7).

Based on these findings and the historical epidemiology of MPX, it is likely that the emergence of the 2022 B.1 outbreak resulted from the continued circulation and evolution of the virus that caused the 2017-2018 Nigerian outbreak. According to the first MPX genome sequences from the 2022 outbreak (3.8), it was shown that phylogenetically these viruses had descended from clade 3 (9). Clade 3 viruses are like those analyzed in 2017-2019 from cases diagnosed in Singapore, Israel, Nigeria, and the United Kingdom (10). However, this is not the case with the A.2 variant, a different lineage from B.1 that descends from clade 3 and possibly has been circulating in Asia before being detected for the first time in 2021 (3). In line with the above, recent analyzes suggest that the A.2 lineage, responsible for the current outbreak in India, may be undergoing a different selection pressure than B.1 (11). This effect could be occurring in other variants not yet identified.

When comparing the genomes of the outbreaks that occurred in Portugal, Belgium, the United States, and Germany with those from the 2017-2018 outbreak, 47 MPX DNA mutations were detected (10). According to the first investigations, the rate of evolution of the smallpox virus is approximately 9x10-6 substitutions per site annually (12). This roughly translates to only 1-2 mutations per year. Therefore, it would be estimated between 2 to 5 genetic alterations for the 4 years of evolution since the last outbreak. The rapid mutations suggest that the 47 substitutions generated between 3-4 years is a higher number than expected (3,10). According to the sequences obtained in the different outbreaks by the MPX, genetic alterations in the virus genome have occurred since the first case in humans (Figure 1). These mutations could confirm the adaptation and sustained transmission currently observed by this virus (10).

Many of the mutations presented in the MPX genetic material that caused the 2022 outbreak were nucleotide changes or substitutions (GA-to-AA). Based on these findings and the sequences of the 2017-2019 outbreak, three amino acid changes (D209N, P722S and M1741I) were evidenced in the MPXV surface glycoprotein called B21 (3,8). These nucleotide changes are characteristic of enzymes from the APOBEC3 family of deaminases (apolipoprotein B mRNA-editing catalytic polypeptide-like 3), which are considered part of the host's innate defense system and with the ability to edit viral DNA (3). The above situation raised two important questions in some authors: First: Did the APOBEC3 changes occur in a non-human animal reservoir host before their appearance in humans? Second: Does this branch of divergence represent a multi-year history of sustained human transmission? (10).

Among the 15 shoot sequences analyzed by Isidro et al (3), they detected the appearance of 15 substitutions. Notably, they all followed the same mutational pattern, including GA > AA and TC > TT, further suggesting a continuous action of APOBEC3 during MPX evolution. Likewise, a subgroup of two sequences that share a deletion was identified. However, gene loss events are not unexpected in Orthopoxviruses. These were observed in the endemic circulation of MPX in Central Africa in 2014, hypothesized to be correlated with increased human-to-human transmission (6).

It is possible that the evidence obtained on the changing epidemiology of human monkeypox could be related to the genetic evolution of MPX. Genomic and phylogenomic analyzes confirm the evolutionary trend of the outbreak strain MPXV 2022, and perhaps shed light on possible mechanisms of human adaptation. However, it is premature to make statements about the possible causes of the mutations and the influence of possible animal reservoirs.

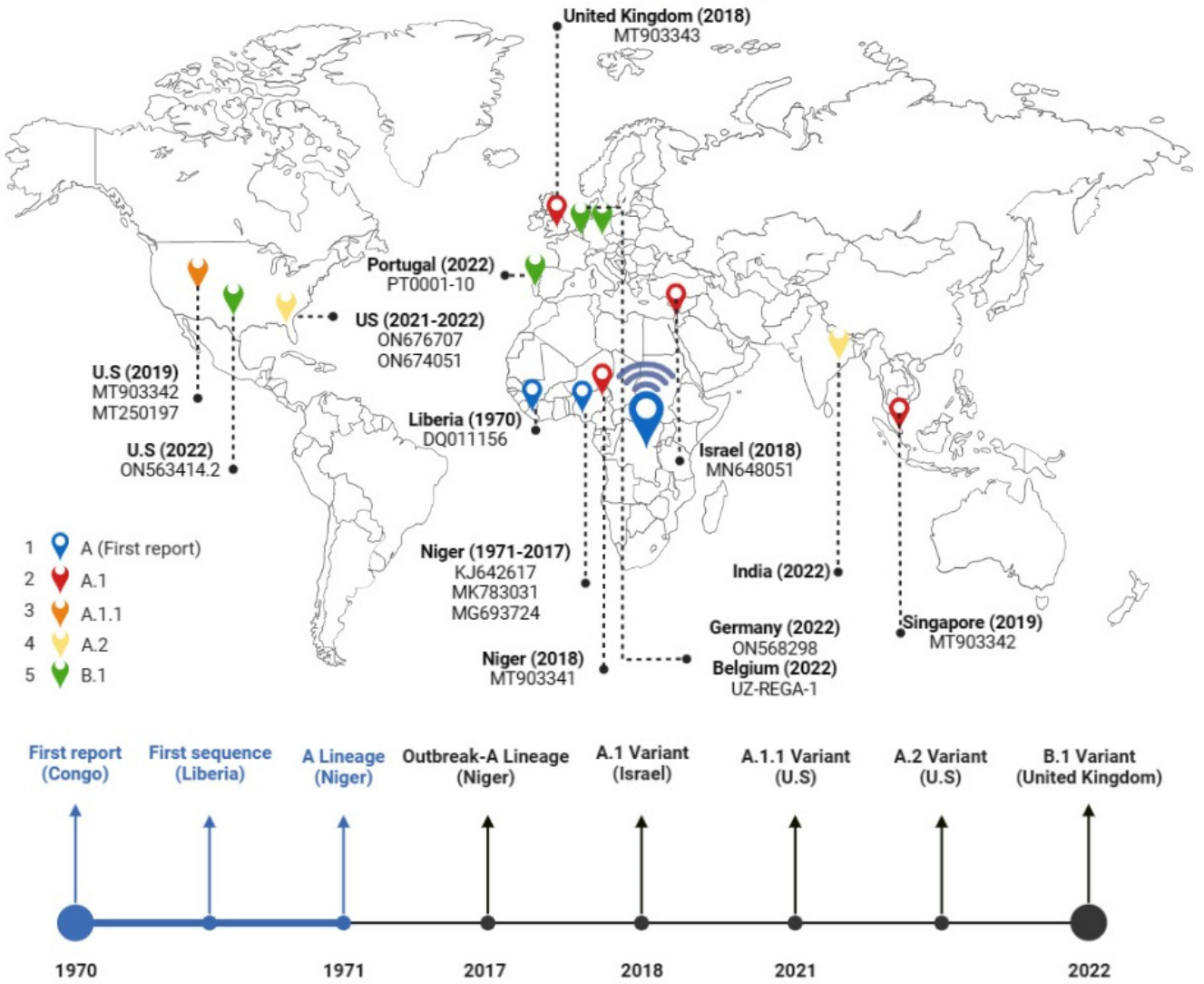

Figure 1. Geographical and chronological distribution of the reported variants of MPXV.PXV.
The lineage is designated according to the nomenclature proposed by Happi et al (9). For the elaboration of the map, the first and main sequences obtained were considered. The timeline describes the first reports of each variant.

Furthermore, the supposed effect of APOBEC3 on the evolution of MPX increases the uncertainty regarding the origins and introductions of the 2022 outbreak (European and Asian) and the complexity of the epidemiological context. This leads to the need for future studies focused on the role of APOBEC3 in the diversification of MPX. Functional studies are needed to assess whether this mutational driver triggers the adaptive evolution of MPX towards altered phenotypic characteristics, such as increased transmissibility (3), a characteristic that MPX presents in the current outbreak.

Phylogenetic analyzes have made it possible to determine that the MPX of the current outbreak belongs to clade 3, which is the most frequent and the lethality is <1%. In contrast, clade 1 viruses are considered more virulent with a lethality >10% (3.9). In epidemiological terms, this could result in increased morbidity but low virulence.

Finally, it is likely that the ongoing outbreak of human monkeypox in non-endemic countries is a consequence of the failure to reduce the spread of the disease in endemic regions of Africa, despite decades of ongoing outbreaks and circulation. active. A globally driven, one-health approach to disease prevention and treatment are considered essential strategies to control current outbreaks and potential future pandemics, even with a changing trend of monkeypox virus evolutionary genetics. human (13).

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