First Human Case of Monkeypox Virus Clade Ia outside Africa

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INTRODUCTION

Monkeypox virus (MPXV) clade Ia, historically associated with sporadic zoonotic transmission in Central Africa, is now demonstrating sustained human-to-human transmission, particularly in Kinshasa, DRC, with possible links to sexual networks[1]. Genomic evidence include the accumulation of APOBEC3-associated mutations. APOBEC3 enzymes are components of innate antiviral immunity. In MPXV, a high burden of these APOBEC3-signature changes is a genomic hallmark of replication in humans and supports sustained person-to-person transmission rather than a solitary zoonotic spillover[1]. In February 2025, Ireland reported the first confirmed MPXV clade Ia case outside Africa in a traveler returning from the DRC (Figure 4).

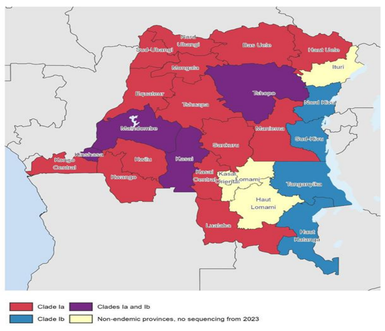

Fig 1. MPXV Clade circulation by region DRC[2].

Fig 2. Lesions caused by infection with MPXV Clade Ia[1].

METHODS

MPXV detection was performed via qPCR using commercial[4] and laboratory developed assays[2], including pan-orthopoxvirus, MPXV clade I/II and clade Ib-specific protocols.

The highest-titre lesion swab was sequenced (Illumina NextSeq 1000) using multiple primer schemes. Reads were processed with the ARTIC MPXV pipeline and aligned to the masked clade Ia reference (KJ642613.1_masked), achieving 100% genome coverage (Pathoplexus accession: PP_002XE2K.1).

Phylogeny was conducted using SQUIRREL (v1.0.12) with 959 sequences from Pathoplexus/GISAID and two outgroups. The run-apobec-phylo option was used to identify mutation characteristics associated with APOBEC3 activity.

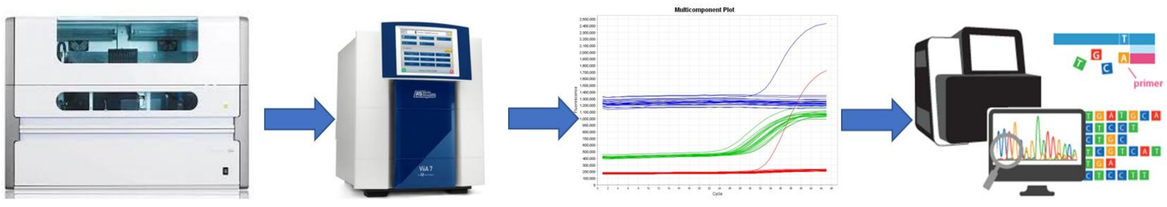

Fig 3: Workflow for MPXV diagnostics.

RESULTS

On 5th February 2025, qPCR testing of clinical samples detected pan-orthopoxvirus DNA and MPXV clade I DNA. Clade Ib and II assays were negative, supporting clade Ia infection (Table 1).

On 10th February Whole Genome Sequencing (WGS) confirmed Clade Ia assignment based on Nextclade analysis and presence of the OPG032 gene.

Phylogenetic analysis placed the Irish sequence within a well-supported cluster (bootstrap = 98%) of 182 clade Ia group II sequences, mostly from Kinshasa, DRC (n = 171), collected in 2024 (Figure 5(a)). Four defining mutations confirmed inclusion in the sustained human 2024 (sh2024) outbreak lineage (Figure 5a).

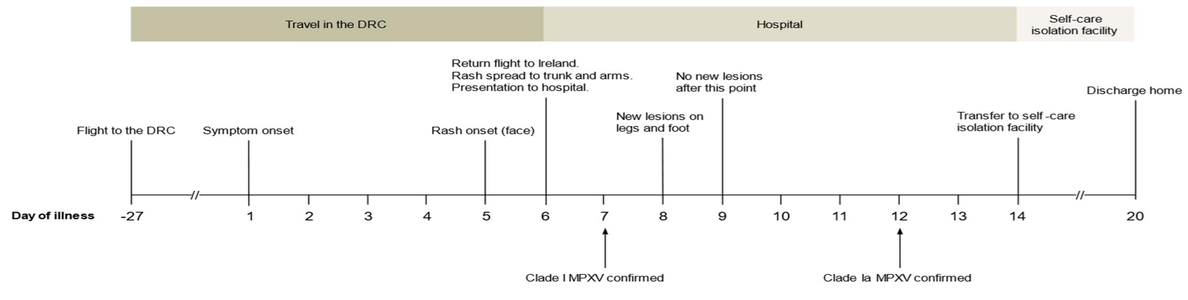

Fig 4. Timeline of key events including MPXV clade Ia detection and confirmation.

Sample type	Date taken	Ct values				
		Pan-othopoxvirus (LDT)	Pan-orthopoxvirus (Altona)	MPXV Clade I	MPXV Clade Ib	MPXV Clade II
Swab (Skin)	04.02.2025	34.95	29.46	34.05	Not Detected	Not Detected
Swab (Skin)	05.02.2025	25.50	22.21	24.34	Not Detected	Not Detected
Swab (Skin)	05.02.2025	25.18	21.44	23.46	Not Detected	Not Detected
Swab (Throat)	05.02.2025	36.33	30.77	34.27	Not Detected	Not Detected

Table 1: Cycle Threshold (Ct) values for samples taken from patient.

The sequence also belonged to a subcluster (n = 21; bootstrap = 99%) of Kinshasa sequences dated 23rd Sept – 7th Nov 2024. Compared to the reference genome (KJ642613.1_masked), it contained 61 SNVs, 10 (16%) of which were linked to APOBEC3 mutational signatures. Of six unique mutations, five (83%) were APOBEC3-associated (Figure 5(b)).

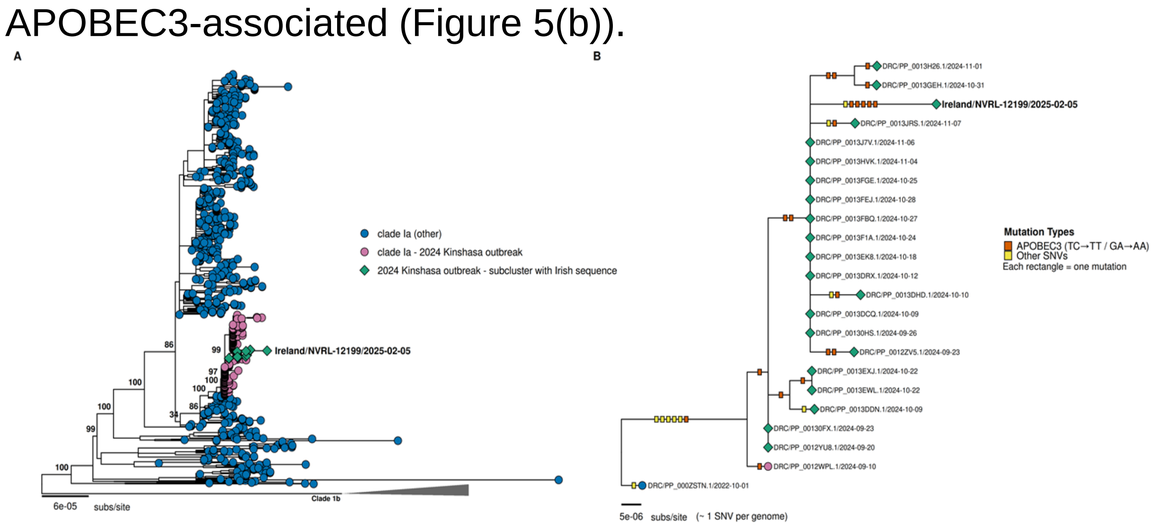

Fig 5 (a) Phylogenetic tree and (b) APOBEC3 mutational profile of the Irish MPXV clade Ia genome.

DISCUSSION

The 2024 MPXV clade Ia outbreak in Kinshasa marks a shift from predominantly zoonotic transmission to sustained human-to-human spread, supported by genomic data showing 68% APOBEC3-type mutations[1]. The Irish case, despite reported wildlife exposure, clusters closely with the Kinshasa sh2024 outbreak strains and harbors a high proportion of APOBEC3-signature substitutions. This supports the likelihood of acquisition via human transmission, rather than an isolated spillover event.

Clinically, the patient experienced a mild, self-limiting illness without complications, and no secondary cases were detected through contact tracing. Importantly, immediate isolation, specialist clinical evaluation, and timely notification of public health authorities upon the patient's arrival in Ireland likely played a critical role in preventing onward transmission.

CONCLUSION

This case highlights a significant epidemiological shift in MPXV clade Ia, with increasing evidence of sustained human-to-human transmission. Recent importations into China and Türkiye further indicate ongoing international spread, emphasising the urgent need for strengthened genomic surveillance, heightened clinical awareness, and coordinated global efforts to monitor and contain emerging outbreaks.

REFERENCES

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