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Fine-Tuning Viral Adaptation through Genome Retraction: Insights from Mpox Outbreaks in South Korea

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BACKGROUND

- Since 2022, the global population has experienced an unusual mpox outbreak, characterized by a distinctive epidemiological pattern involving dense sexual network partnerships within specific populations. This epidemiological context led to an initial rapid outbreak driven by exclusive human-to-human transmission, facilitating a broader scope of viral evolution than initially anticipated.

- For national variant surveillance, genomic analysis was conducted on samples from mpox-positive cases in South Korea between 2022 and 2024. A total of 138 cases were analyzed, and five novel instances of genome deletion were identified.

METHODS

- **Sample Collection & Viral Genome Sequencing**
  Viral genomes were extracted from clinical specimens of mpox-confirmed cases in South Korea (2022–2024). Long-read sequencing (Nanopore) using a metagenomic approach and short-read sequencing (Illumina MiSeq) with probe-based hybridization to enrich the virus of interest were performed for comprehensive genomic analysis.

- **Genome Assembly & Variant Analysis**
  High-quality genome assembly was performed using Unicycler, Hybractor, and Flye for short-read and long-read data. Reference genome (NC_063383.1) mapping and de novo mapping were carried out using CLC Genomics Workbench 20 (CGW20), followed by detailed variant analysis, including the detection of genomic deletions.

- **Functional Analysis & Comparative Study**
  The functional impact of identified genomic deletions was assessed and compared to existing datasets.

ADDITIONAL KEY INFORMATION

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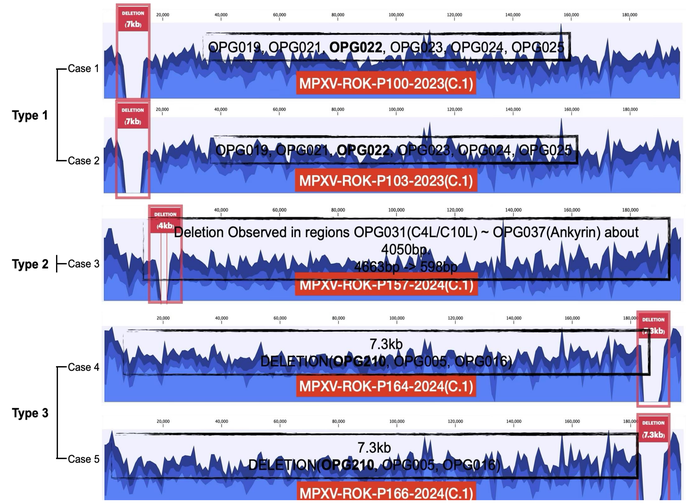
Main Finding

1. Transmission Heterogeneity and Molecular Evolution:
The 2022–2024 mpox outbreak in South Korea was marked by *transmission heterogeneity*, particularly within MSM communities. In response to selective pressures from sustained outbreaks, *the virus accumulated mutations and genomic deletions, enhancing its adaptability and transmissibility.*

2. **Genomic Deletions, Immune Evasion, and Adaptive Strategies:**
Genomic surveillance identified five key deletions in functional regions, including growth factors, apoptosis inhibitors, IL-18 binding, NF-κB inhibition proteins, BCL-2-like proteins, and virulence factors, suggesting a potential role in immune regulation and viral adaptation.

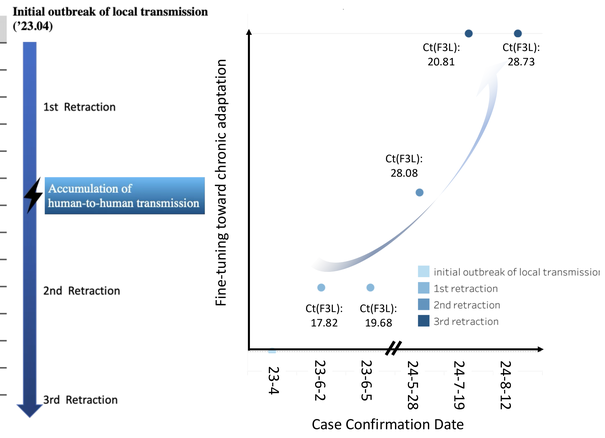
3. **Co-evolution with the Host:**
Rather than completely suppressing immune responses, these deletions likely fine-tune viral-host interactions, promoting a balance that supports long-term persistence and co-evolution.

RESULTS 1. Identification of Five Genomic Deletions During the 2022–2024 Mpox Outbreak in South Korea



RESULTS 2. Functional Implications of Genomic Deletions Identified in the 2022–2024 Mpox Outbreak: Genomic Region and Description.

	OPG	Description	Reference
Type 1	019	Viral growth factor	Viruses. 2023; 15(4):995.
	021	Apoptosis inhibitor	Viruses. 2023; 15(4):995.
	022	IL-18 binding protein	Viruses. 2023; 15(4):995.
	023	Viral growth factor, Ankyrin-like protein, De novo deletions in MPXV Clade IIb B.1 genomes	mSphere 9:e00576-24. Viruses. 2023; 15(4):995.
	024	Unknown	
	025	Ankyrin-like protein	mSphere 9:e00576-24. Viruses. 2023; 15(4):995.
Type 2	031	NF-kB inhibition, apoptosis inhibitor, C4L	mBio 14:e00408-23.
	034	TLR-signal inhibitor, BCL-2 domain	mSphere 9:e00576-24.
	035	Inhibitor of IRF3, NF-kB activation, apoptosis inhibitor, BCL-2-like protein	Viruses. 2023; 15(4):995.
	036	N2L, innate immune modulator, virulence factor gene	Nat Commun 15, 7452
	037	ANK repeat containing protein; prevents apoptotic functions of the apoptosome, O1L	Virus Evolution, 2023, 9(1), vead031
Type 3	005	BCL-2 domain, Host range factor, C16L/B22R	mSphere 9:e00576-24.
	210	Surface glycoprotein, T cell response suppressor, virulence factor, B22R family protein	mSphere 9:e00576-24.
	016	MHC class 1 homolog, blocks NKG2D receptor, OMCP	mSphere 9:e00576-24.



1st Retraction: Impairment of immune evasion mechanisms: simultaneously playing opposing roles of initial immune evasion failure and promoting viral spread.

2nd Retraction: Immune signal modulation: Induces changes in host immune system interactions, facilitating the persistence and spread of infection.

3rd Retraction: Adaptation to persistent infection through virulence modulation(co-evolution).

CONCLUSIONS

- Although the sample size is limited, the affected regions are functionally significant, suggesting genome retraction as a potential mechanism of viral adaptation. Initially, these deletions may have impaired immune evasion mechanisms, paradoxically both limiting immune escape and facilitating viral spread. However, as human-to-human transmission continued, the virus progressively accumulated deletions in virulence factors, potentially reducing virulence while enhancing co-evolution with the host.

- If the virus adopts a strategy favoring reduced virulence and long-term persistence, traditional surveillance methods may be insufficient. Alternative approaches, such as wastewater surveillance and proactive monitoring systems, will be essential for effective public health responses.

- Further research is needed to functionally validate how these deletions regulate immune responses from the host transcriptome perspective, while cytokine analysis will help elucidate their impact on pathogenicity, host adaptation, and immune modulation.