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Review Article

Genomic Insights into Monkeypox Virus: Paving the Way for Targeted Vaccine Development and Therapeutic Targeting

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Abstract

Monkeypox virus (MPXV), a zoonotic orthopoxvirus, has emerged as a growing global health concern due to its expanding geographic spread and sustained human-to-human transmission. Advances in whole-genome sequencing have enabled detailed characterization of the MPXV genome, revealing a conserved central region essential for replication and variable terminal regions associated with host adaptation, immune evasion, and virulence. Comparative genomic analyses distinguish the more virulent Congo Basin (Clade I) lineage from the less severe West African (Clade II) lineage, reflecting differences in transmission dynamics and clinical outcomes. Integrating genomic data with structural and immunological insights has facilitated the identification of conserved viral targets for vaccine and therapeutic development, including monoclonal antibodies directed against key antigenic determinants. In parallel, next-generation vaccine platforms such as mRNA, DNA, and recombinant viral vectors are advancing MPXV prevention strategies and complementing existing orthopoxvirus vaccines. These innovations offer improved safety, scalability, and adaptability to emerging variants. This review highlights the interplay between viral genomics, evolution, and host immune responses, underscoring their importance in guiding rational vaccine design and targeted therapeutics. Continuous genomic surveillance and multidisciplinary research efforts remain critical for improving outbreak preparedness and mitigating the public health impact of MPXV.

Keywords: *Antiviral Therapies; Monkeypox Virus (MPXV); Vaccine Development; Zoonotic Diseases*

Introduction

The global health landscape has been marked by the re-emergence and spread of zoonotic diseases, which has raised concerns about preparedness and response capabilities. Among these monkeypox and orthopoxvirus with significant genetic and clinical parallels to smallpox has just resurfaced as a public health threat beyond its endemic regions in Central and West Africa (Shehryar *et al*., 2023; Singh *et al*., 2024). The virus, first identified in 1958 in laboratory monkeys has evolved from an obscure regionally confined ailment into an infection with global implications. This shift is driven by various factors including ecological changes, human encroachment on wildlife habitats, and the decrease in smallpox vaccination coverage following the eradication of smallpox. These circumstances have created a need for a deeper understanding of monkeypox virus (MPXV) and the evolution of targeted medical procedures (Xiang & White, 2022). At the forefront of this endeavour lies the field of genomics, which has become an invaluable tool for unravelling the molecular intricacies of infectious agents. Genomic analysis allows scientists to dissect the genetic architecture of pathogens, shedding light on their evolution, virulence factors, transmission dynamics, and interactions with the host immune system.

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For monkeypox, genomic insights offer a gateway to developing targeted vaccine platforms and designing precise antiviral therapies (Bianconi *et al*., 2023). Rapid developments in bioinformatics and sequencing technology have broadened the field of genomic research in recent years, enabling researchers to detect new genetic markers, trace the genetic evolution of MPXV strains, and anticipate possible shifts in virulence and transmissibility (Harini *et al*., 2026). Monkeypox presents with clinical features that overlap with other poxvirus infections including fever, rash, and lymphadenopathy, yet its clinical and epidemiological profile shows important distinctions that necessitate specific public health strategies. For instance, unlike smallpox, monkeypox maintains an animal reservoir, complicating its elimination and control efforts. The virus is divided into two primary clades: the Central African (Congo Basin) clade, which has greater virulence and transmission capacities, and the West African clade, which is linked to milder sickness and lower death. Understanding the genomic differences between these clades has profound implications for both vaccine development and therapeutic approaches guiding tailored responses to outbreaks based on the predominant strain. Genomic studies have unveiled key features of the MPXV genome revealing it to be a large, virus of double-stranded DNA that is about 197 kilobases in size. Unlike RNA viruses that mutate rapidly, DNA viruses such as MPXV generally exhibit lower mutation rates due to their more robust replication machinery. However, this does not preclude genomic variation altogether recombination events and selective pressures can still drive genetic diversification (Monzón, *et al*., 2024). Detailed genomic mapping of MPXV has identified conserved and variable gene regions, including those linked to immune evasion, host specificity, and pathogenesis. Insights from these genomic analyses, as illustrated in Figure 1, have provided a foundation for identifying potential targets for vaccines and antiviral drugs, enabling more efficient and targeted research efforts (Li *et al*., 2024). The development of effective vaccines against monkeypox has benefited from the historical success of smallpox vaccines which demonstrate cross-protection due to the antigenic similarities between the two viruses. However, concerns over safety particularly in immunocompromised individuals, and the potential for waning immunity over time underscore the need for more targeted vaccine candidates. Genomic data has been pivotal in guiding the design of next-generation vaccines that are safer and tailored to elicit robust and long-lasting immunity. By understanding which genetic elements are crucial for viral replication and immune response activation, researchers can refine vaccine constructs to maximize efficacy and safety (Hirani *et al*., 2023). Therapeutic targeting of monkeypox also stands to gain from genomic insights. The identification of genes connected to medication resistance or host pathogen interactions can inform the development of targeted antiviral therapies.

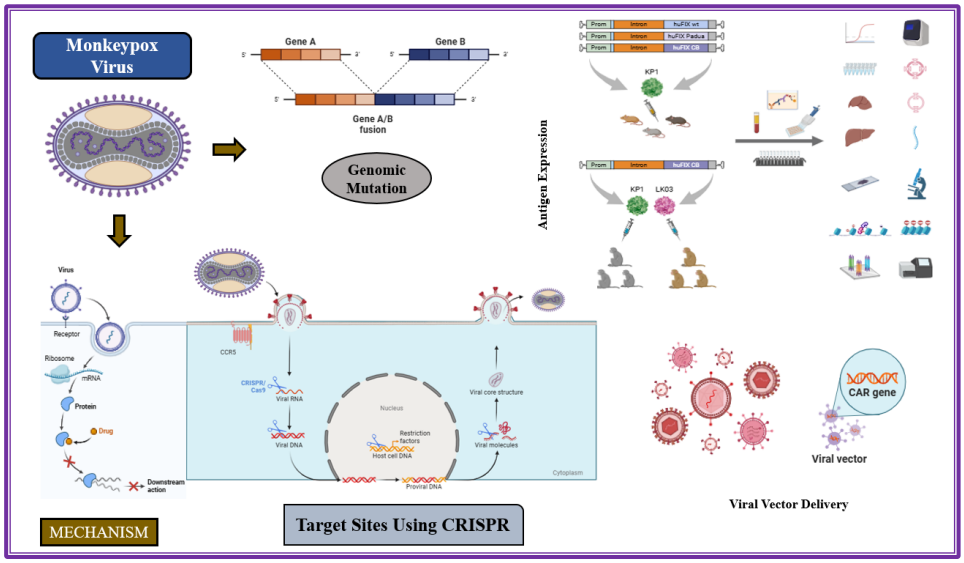


***Figure 1**: Genomic Mutations, Antigenic Variability, CRISPR Based Target Identification, Viral Replication, and Viral Vector Mediated Gene Editing and Immunotherapy in Monkeypox Virus (MPXV).*

Existing antiviral agents, such as tecovirimat and brincidofovir, have shown efficacy against orthopoxvirus but their performance specifically against different MPXV strains requires further investigation (Lu *et al*., 2023). Genomic analysis can reveal strain specific variations that impact the effectiveness of these treatments, thereby facilitating the optimization of therapeutic protocols and the discovery of new drug candidates (Lum *et al*., 2022). As the world faces the continuous threat of infectious diseases integrating genomic data into public health strategies provides a strategic advantage. This approach not only enhances the precision of diagnostic tools but also accelerates the research and development pipeline for medical countermeasures. The COVID-19 pandemic demonstrated the power of genomics in tracking viral evolution and informing vaccine updates offering a blueprint for addressing monkeypox and other emerging diseases (Olawade *et al*., 2024). The intricate molecular interplay orchestrating the initial stages of a Monkeypox Virus (MPXV) infection is a masterclass in viral strategy, where a carefully choreographed engagement with host cell receptors dictates both cellular tropism and pathogenic outcome (Quan *et al*., 2025). This process transcends simple attachment, embodying a multi-layered and redundant approach that ensures robust entry across diverse cell types. The initial, low-affinity docking is predominantly mediated by viral membrane proteins, such as H3 and D8, which bind with high avidity to ubiquitous glycosaminoglycans (GAGs) like heparan sulfate, effectively concentrating viral particles on the cell surface and increasing the probability of a more committed interaction (Chao *et al*., 2024; Sobhy, 2017). This preliminary tethering is swiftly consolidated by a higher-affinity binding event, notably between the viral A27L and E9L protein and the non-integrin laminin receptor, a widely expressed cellular adhesion molecule that serves as a central portal for poxvirus entry (Loganathan *et al*., 2024). Beyond this fundamental entry pathway, MPXV exhibits a cunning dimension of immune subterfuge by selectively targeting immunomodulatory receptors such as CD209 (DC-SIGN) on dendritic cells and macrophages (Andrieu *et al*., 2025). This connection does more than just facilitate viral entry into these pivotal sentinel cells, it actively exploits their normal trafficking and signaling pathways, potentially impairing antigen presentation and co-stimulation, thereby blunting the nascent adaptive immune response before it can fully mobilize (Howard *et al*., 2022). This elaborate symphony of receptor usage, combining broad-spectrum attachment molecules with specific entry portals and immunoregulatory targets, fundamentally explains MPXV's capacity for widespread tissue dissemination and its successful establishment of a foothold within the immunologically competent host (Puagsopa *et al*., 2025). Recent years have seen the development of novel vaccination alternatives against MPXV, including cutting-edge multivalent mRNA and DNA vaccines based on the identification of immunogenic proteins from the MPXV capsid. To ensure global population safety, this review will analyze the latest advancements in mpox vaccine production, providing a critical overview of these new technologies and highlighting the urgent need to push the boundaries of research and development in order to produce vaccines that can provide strong immune responses, long-lasting protection, a noticeable reduction in symptoms, effective virus neutralization, and complete disease prevention.

Genomic Structure of Monkeypox Virus

Members of the Poxviridae family, the Chordopoxvirinae subfamily, and the Orthopoxvirus genus include the Monkeypox virus (MPXV) or (MPV Metapneumovirus) (Farasani, 2022). The MPXV appears to be huge when viewed using electron microscope (200-250 nanometers). Orthopoxviruses share a highly conserved antigenic makeup and genetic architecture, which explains the strong cross-protective immunity observed among members of this genus (Howard *et al*., 2022). This conservation arises from a central genomic core that encodes essential viral functions, including replication enzymes, structural proteins, and morphogenesis factors. The conserved and variable genomic features relevant to vaccine and therapeutic target selection are summarized in Table 1. Despite this shared genetic foundation, orthopoxviruses differ significantly in their host range and pathogenicity due to variation in the terminal regions of the genome, where species-specific genes governing virulence, immune evasion, and host adaptation are located (Puagsopa *et al*., 2025). Gene loss, duplication, and recombination events in these terminal regions enable viruses such as Variola virus (strictly human-specific) to exhibit distinct host specificity, while Cowpox virus and Monkeypox virus retain broader host-range genes that allow

infection across multiple mammalian species (Gieryńska *et al*., 2023). Thus, while orthopoxviruses remain antigenically similar, diversity in their accessory gene repertoire leads to substantial differences in disease severity, transmissibility, and host tropism (Sagdat *et al*., 2024). Poxviruses are brick-shaped viruses that have a lipoprotein sheath surrounding their linear, double-stranded DNA genome. Poxviruses have genomes that contain all the proteins needed for assembly, replication, transcription, and egress, even though they depend on host ribosomes for mRNA translation. It has been demonstrated that a few viruses in the Orthopoxvirus genus and Poxviridae family, including MPXV, cowpox virus (CPXV), variola virus (VARV), and vaccinia virus, can infect people (Kugelman *et al*., 2014). Orthopoxviruses share a common antigen and genetic composition but differ in their host range and pathogenicity traits. Evolution is an ongoing process that can be influenced by the host species' selection pressure. Progressive gene loss, particularly around the ends of the genome, has been suggested as the driving force behind many viruses. MPXV has a 197 kb linear DNA genome with 190 nonoverlapping Open Reading Frames (ORFs) longer than 180 nt. (Lu *et al*., 2023). MPXV, a novel Orthopoxvirus MHC Class I-like Protein (OMCP) virus, has at least four ORFs in its ITR region, which is affected by genomic instability and genetic variation. It appears to be evolving for effective human replication given the link between secondary transmission and gene loss. Factors like vaccination status and human encroachment on reservoir ecosystems may also contribute to the introduction of variation and enhanced human-to-human transmission. The zoonotic and human-to-human transmission routes are illustrated in Figure 2. West African (clade II) and Congo Basin (clade I) are the two genetic clades into which the virus is divided. 95% of regional clusters and 99% of geographical areas are identified using genetic sequences (Rabaan *et al*., 2023).

Table 1: *Conserved And Variable MPXV Genomic Features, Their Biological Functions, and Their Implications for Vaccine and Therapeutic Target Selection*

Genomic Feature / Target	Functional Role in MPXV Biology	Implications for Vaccines / Therapeutics	References
B21R gene (Immunomodulatory protein)	Facilitates immune evasion by downregulating host immune signaling.	Important target for designing vaccines that neutralize immune-evasion pathways.	Jahankir *et al*., 2024
A35R protein (Membrane-associated protein)	Supports viral entry and release, influencing transmissibility.	Considered for antigen selection in recombinant vaccines.	Roper, 2006
A33R & B5R proteins (Envelope proteins)	Promote virion attachment and dissemination in host tissues.	Highly conserved; strong neutralizing antibody targets in next-generation vaccines.	Ntombela *et al*., 2023; Wang *et al*., 2023
L1R protein (Entry-associated protein)	Essential for mature virion formation and host cell entry.	Incorporated into multivalent vaccines due to high immunogenicity.	Ntombela *et al*., 2023
A27L protein (Heparan sulfate-binding protein)	Mediates virus attachment to host cell GAG receptors; enhances tropism.	Structural studies support its inclusion as a conserved antigen for vaccine design.	Zeng *et al*., 2023
E9L gene (Viral DNA polymerase)	Core enzyme for viral genome replication.	Primary antiviral target; inhibited by brincidofovir and cidofovir.	Zeng *et al*., 2023
VP37 protein (Required for extracellular virion formation)	Supports virion egress and dissemination.	Target of tecovirimat; remains highly conserved across MPXV strains.	Gigante *et al*., 2024; Russo *et al*., 2021

The genomic sequence of the mpox virus from an infected Portuguese man was discovered in a recent study. On May 4, 2022, a swab sample was taken from the patient's skin lesions (Alakunle *et al*., 2020). According to phylogenetic analysis, the sequence was a member of the West African branch. According to research, the virus most closely resembled viruses linked to earlier Nigerian exports to other nations in 2018 and 2019. The reference sequence comprises approximately 92% of the length of the draft sequence. However, according to WHO, there is no proof that the MPXV has altered (Wruck & Adjaye, 2021). It was found that the MPXV-USA-2003-039 (human) and MPXV-USA-2003-044 (prairie dog)

viruses share a common origin and differ by a single nucleotide (Araf *et al*., 2024). The phylogenetic separation between Clade I and Clade II MPXV reflects not only geographic isolation, but also functional divergence driven by historical ecological dynamics. Clade I, circulating predominantly in Central Africa, shows signatures of stronger selective pressure related to host immune evasion, which aligns with its higher virulence and increased capability for sustained transmission (Souza *et al*., 2023). Clade II strains, which have historically circulated in West Africa, show reduced virulence markers but enhanced traits that facilitate human-to-human spread, as evidenced by the 2022 global outbreak (Bruneau *et al*., 2023). Including MPXV within a broader orthopoxvirus phylogeny demonstrates its evolutionary proximity to both VACV and VARV, while also illustrating the ancestral branching from more genetically diverse viruses such as CPXV. These evolutionary patterns support hypotheses that MPXV may be undergoing ongoing adaptation as ecological and human behavioral factors shift (Shi *et al*., 2025).

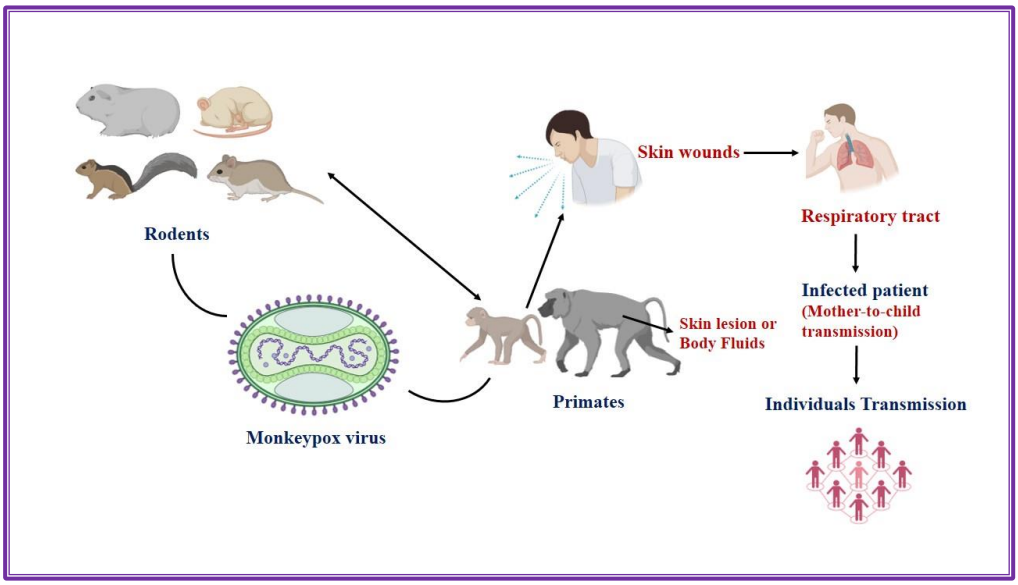


Figure 2*: Monkeypox Virus Transmission Cycle: Reservoir Hosts, Zoonotic Spillover, Routes of Human Infection, and Community-Based Outbreak Propagation.*

Poxviruses are large, enclosed DNA viruses that grow inside the cytoplasm of vertebrate or invertebrate cells. Within the Poxviridae family, the Orthopoxvirus genus contains a few zoonotic viruses, such as variola, vaccinia, cowpox, and mpox (Saravanan *et al*., 2022). The replication cycle of the poxvirus demonstrates how mpox reproduces. Viral-encoded proteins are how poxviruses replicate in the cytoplasm. The infectious poxvirus's DNA, proteins, and enzymes are found in its core. Late gene expression (MV) is followed by the viral assembly process, which creates mature viruses, the first infectious form (Moss *et al*., 2013). When the outer and plasma membranes combine, extracellular virions (EVs), which depend on 11-12 nonglycosylated transmembrane proteins, are released. MVs have a stable outer membrane, whereas EVs have a loose one and are designed to spread inside the host (Doyle & Wang, 2019). The virostealth and virotransducer action of poxvirus proteins prevent the cell from reacting to the infection. The host's immune system's capacity to identify viruses can be weakened by viromimic proteins, such as virostealth proteins. Certain extracellular viromimic proteins control immune responses (Moss *et al*., 2012). Baroreceptors inhibited the function of host cytokines and chemokines by competitively binding them. By producing viral mimics of host growth factors, cytokines, and chemokines, Virokines successfully eliminate host immune responses that prevent viral survival and encourage viral growth and spread. To go around and elude the host immune system, these modulatory proteins (poxviral B22 family proteins) work together (Hasan & Saeed, 2022; Alcami *et al*., 2003).

Advancements in Genomic Sequencing of MPXV

Advances in sequencing technologies have dramatically enhanced the ability to map and study the MPXV genome, facilitating faster and more accurate tracking of viral evolution. Traditional Sanger sequencing, while historically significant, was labor-intensive and time-consuming (Satam *et al*., 2023). Next-generation sequencing (NGS) platforms like Illumina and Ion Torrent changed the industry by offering high-throughput capabilities that provide thorough genomic data faster (Gupta & Verma, 2019). These methods, as summarized in Table 2, have enabled the detailed assembly of the MPXV genome, revealing patterns of mutation, recombination, and adaptation across different outbreaks. Long-read sequencing technologies, including PacBio, Oxford Nanopore have further enriched these insights by uncovering structural variations like insertions, deletions, and complex rearrangements often missed by short-read methods (Vandenbogaert *et al*., 2022). These structural details can impact viral virulence, host range, and immune evasion strategies, providing a deeper understanding of how MPXV evolves and adapitates under selective pressures. During recent outbreaks, genomic sequencing has allowed scientists to monitor real-time changes in the virus, identifying mutations that could influence its transmissibility and virulence (Veeraraghavan *et al*., 2023). Recent research on emerging viral pathogens shows that integrating genomic, structural, and host- interaction data is essential for understanding viral evolution and adaptation. Rapid mutations, particularly in surface proteins, can alter receptor binding, host range, and immune escape. Computational modelling and structural simulations further predict how specific amino acid changes may influence virulence or immune recognition. These insights are directly relevant to Monkeypox virus, which continues to acquire lineage-specific mutations linked to transmissibility and host adaptation. Together, they strengthen real-time MPXV surveillance and guide the development of targeted diagnostics, vaccines, and therapeutics (Yadav *et al*., 2025; Yi *et al*., 2024; Wang *et al*. ,2025). This rapid identification of genetic variations has enabled public health officials to tailor response strategies more effectively, such as adjusting vaccine formulations to match circulating strains and predicting potential resistance to antiviral agents (He *et al*., 2023).

Table 2: *Comparative Overview of Sequencing Approaches Used in MPXV Genomic Surveillance, Including Sanger Sequencing, Short-Read NGS Platforms, and Long-Read Sequencing Technologies, With Their Principal Contributions to Genomic Analysis*

Sequencing Technology	Key Features	Contribution to MPXV Genomic Research	References
Sanger Sequencing	High accuracy, low throughput	Enabled early characterization of MPXV genome; foundational for comparing clade differences.	Satam *et al*., 2023
Illumina NGS (Short-Read)	High depth, rapid parallel sequencing	Provided comprehensive coverage of MPXV mutations, recombination patterns, and outbreak lineage tracing.	Gupta & Verma, 2019; Veeraraghavan *et al*., 2023
Ion Torrent NGS	Semiconductor-based detection	Used for rapid and cost-efficient genome scanning during outbreak surveillance.	Gupta & Verma, 2019
PacBio SMRT Sequencing	Long reads, high accuracy	Revealed structural variations, deletion/duplication events in terminal genome regions.	Vandenbogaert *et al*., 2022
Oxford Nanopore Sequencing	Ultra-long reads, portable devices (MinION)	Enabled real-time field sequencing; identified insertions, deletions, and genome rearrangements in MPXV samples.	Vandenbogaert *et al*., 2022
Hybrid Sequencing (Illumina + Nanopore)	Combines accuracy and long-range continuity	Produced complete high-resolution MPXV genomes including inverted terminal repeats and accessory genes.	Vandenbogaert *et al*., 2022; Yadav *et al*., 2025
AI-driven Genomic Analytics	Machine learning for mutation prediction	Predicted lineage-specific mutations, antigenic drift patterns, and potential antiviral resistance.	Najafi *et al*., 2022

Current Diagnostic Approaches and Their Limitations

Current diagnosis of mpox relies primarily on nucleic acid amplification testing, especially real-time PCR, using lesion material such as skin, fluid, or crusts as the preferred specimens. When lesions are absent, oropharyngeal, genital, anal, or rectal swabs may be considered, although negative results from these alternative specimens may not reliably exclude infection. Other approaches include clade-specific molecular assays, whole-genome sequencing for epidemiological and evolutionary characterization, antigen detection, serology, and virus isolation. However, these methods have important limitations: PCR requires trained personnel, laboratory infrastructure, and specialized equipment; specimen quality and timing can affect sensitivity; sequencing is comparatively resource-intensive and is primarily used for surveillance rather than routine diagnosis; antigen assays may have variable sensitivity and require further validation; serology cannot reliably distinguish MPXV exposure from other orthopoxvirus infections and is therefore unsuitable as a stand-alone diagnostic test; and virus isolation is not recommended as a routine clinical diagnostic method because of biosafety and infrastructure requirements. These limitations support continued development of rapid, decentralized molecular and CRISPR-based point-of-care assays that can complement, rather than immediately replace, validated PCR testing (Liu *et al*., 2024; CChen *et al*. 2025; Centers for Disease Control and Prevention, 2026).

Genomic Variations and Their Impact

Genomic variations within MPXV play a crucial role in determining its transmissibility, virulence, and potential resistance to antiviral treatments. Specific mutations in the viral genome can enhance the virus's ability to spread and survive within the host environment (Yi *et al*., 2024). For example, changes in the B21R gene, which codes for an immune-modulatory protein, have been linked to alterations in the virus's capacity to evade host immune responses. This gene allows the virus to downregulate immune signaling pathways, diminishing the host's ability to mount an effective response (Jahankir *et al*., 2024). Similarly, mutations in the A35R gene responsible for membrane protein expression can impact the virus's efficiency in entering and exiting host cells, directly influencing its transmission rate. The identification of these mutations and their functional implications, summarized alongside antigenic targets and clade differences in Table 3, is essential for assessing the virus's potential threat and developing targeted vaccines that neutralize these enhanced capabilities (Roper, 2006). Resistance to antiviral drugs can also emerge through mutations, particularly those affecting the viral DNA polymerase gene, which is targeted by nucleoside analogs like cidofovir and brincidofovir. Monitoring for mutations in this region can inform the development of next-generation antiviral drugs that maintain efficacy in the face of evolving viral resistance (Tilloy *et al*., 2024). Additionally, the VP37 protein a target of the antiviral tecovirimat has remained highly conserved across MPXV strains, underscoring the potential for stable treatment regimens. However, genomic surveillance remains crucial to detect any variations that might affect drug binding and effectiveness (Gigante *et al*., 2024).

Table 3: *Integrated Overview of Major MPXV Genomic Variations, Key Antigenic Targets Relevant for Vaccine Development, And Critical Genomic Differences Between Clade I And Clade II. This Table Connects Genomic Mutations to Functional Outcomes and Immunological Relevance. It Provides a Concise Framework Linking MPXV Evolution with Therapeutic and Vaccine Design.*

Category	**Feature / Gene / Antigen**	**Functional Role**	**Implications for Vaccines / Therapeutics / Viral Behavior**	**References**
Genomic Variations & Functional Consequences	B21R (Immunomodulator)	Suppresses host immune signaling	Mutation enhances immune evasion; important for surveillance	Jahankir *et al*., 2024
	A35R	Membrane protein regulating virion egress	Impacts transmissibility; candidate for recombinant vaccines	Roper, 2006
	APOBEC3-driven mutations	Host-mediated antiviral editing	Increases mutation rate, shaping viral evolution	Jahankir *et al*., 2024

	DNA polymerase (E9L)	Viral DNA replication	Determines susceptibility to brincidofovir/cidofovir	Zeng *et al*., 2023
	VP37 (F13L)	Required for extracellular virion formation	Drug target of tecovirimat; remains highly conserved	Gigante *et al*., 2024; Russo *et al*., 2021
	Terminal Inversion Mutations	Occur in ITR regions	Impact host range, adaptation, and virulence	Lu *et al*., 2023; Rabaan *et al*., 2023
Antigen Targets for Vaccine Platforms	A33R & B5R	Envelope proteins for virion spread	Highly conserved; major neutralizing antibody targets	Ntombela *et al*., 2023; Wang *et al*., 2023
	L1R	Mature virion membrane protein	Promotes strong neutralizing antibody responses; included in next-generation vaccines	Ntombela *et al*., 2023
	A27L	Glycosaminoglycan -binding protein	Enhances host cell attachment; structural insights used for protein vaccine design	Zeng *et al*., 2023
	D8L	Binds chondroitin sulfate	Important for entry; being evaluated for epitope-based vaccines	Sobhy, 2017
	A29L, H3L	Surface antigens	Used in multi-antigen mRNA and recombinant vaccines	Zeng *et al*., 2023
Clade I vs. Clade II Comparative Genomics	Virulence-associated genes	Clade I contains more active immunomodulatory genes	Explains higher severity of Central African clade	Souza *et al*., 2023
	Transmission-related genes	Clade II shows adaptation toward human-to-human spread	Correlates with 2022 global outbreak patterns	Bruneau *et al*., 2023
	Accessory gene deletions	More gene loss observed in Clade IIb	Potential adaptation for efficient human replication	Rabaan *et al*., 2023; Shi *et al*., 2025
	Genetic diversity	Clade I more genetically stable	Clade II accumulates APOBEC3 mutations more rapidly	Bruneau *et al*., 2023; Jahankir *et al*., 2024
	Cross-reactive antigens	Highly conserved across both clades	Enables effectiveness of broad orthopoxvirus vaccines like MVA	Gao *et al*., 2023

Implications for Vaccine Development

The development of vaccines tailored to MPXV has benefited significantly from genomic insights leading to more targeted and effective immunization strategies. The identification of conserved viral antigens through genomic studies has paved the way for designing vaccines that elicit strong, long-lasting immune responses (Garcia-Atutxa *et al*., 2024). Proteins such as A33R and B5R, which are involved in viral attachment and dissemination, have been highlighted in Table 1 as prime targets due to their conservation across different MPXV strains. These proteins have demonstrated their ability to induce neutralizing antibodies, forming the basis for vaccine candidates (Wang *et al*., 2023; Ntombela *et al*., 2023). Additionally, the L1R protein known for its role in viral entry has been included in experimental vaccines to stimulate a robust immunogenic response. Vaccine platforms have evolved to leverage these genomic findings. Live-attenuated vaccines, such as the Modified Vaccinia Ankara (MVA), provide cross-protection against MPXV due to its genetic similarity with other orthopoxviruses (Gao *et al*., 2023). Genomic analyses support the use of MVA by demonstrating its stability and minimal risk of reversion to virulence. Recombinant protein vaccines, which express specific MPXV antigens identified through genomic research, offer a targeted approach that can be updated to reflect genetic changes observed in circulating strains. The adaptability of mRNA vaccine technology also presents an opportunity to rapidly encode newly identified antigens, enabling swift responses to evolving MPXV clades (Byrareddy *et al*., 2023).

Therapeutic Targeting Based on Genomic Insights

The treatment of MPXV infection has also seen significant advances driven by genomic studies which have identified potential new targets for antiviral development. Existing antivirals like tecovirimat and brincidofovir work by disrupting viral processes crucial for replication and dissemination (Russo *et al*., 2021). The three-dimensional structures shown in Figure 3 illustrate A27L and E9L, which are relevant to viral attachment and DNA replication, respectively. Tecovirimat, for instance, targets the VP37 protein which is essential for the formation of extracellular virions. Genomic studies have confirmed the protein's conservation across different MPXV strains, suggesting that this antiviral will likely remain effective despite potential mutations. Brincidofovir inhibits viral DNA synthesis by targeting DNA polymerase, a critical enzyme encoded within the MPXV genome (Hirani *et al*., 2023).

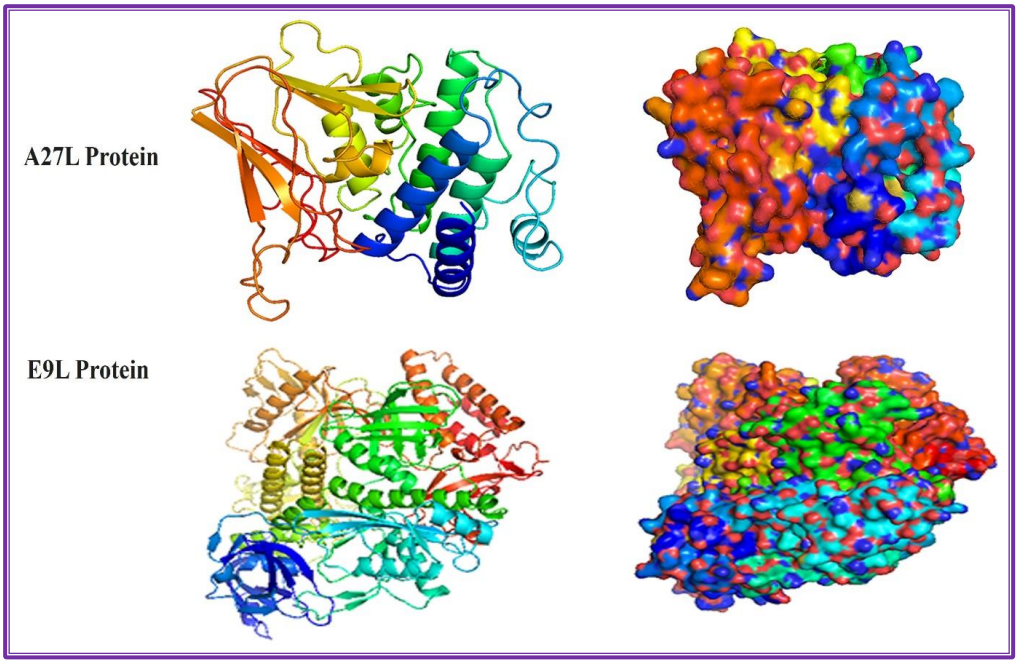


Figure 3: *Three-Dimensional (3D) Structural Representation of A27L And E9L Proteins of the Monkeypox Virus*

Challenges in Monitoring Genomic Evolution

While the advancements in genomic sequencing and analysis have provided significant insights into the monkeypox virus, challenges remain in effectively monitoring its evolution on a global scale. One of the main obstacles is the limited availability of genomic surveillance infrastructure in regions where MPXV is endemic (Nyame *et al*., 2023; Hill *et al*., 2023). The disparity in resources and funding means that many outbreaks are not fully sequenced or documented, leading to potential gaps in understanding the virus's genetic diversity and its adaptation mechanisms. Additionally, the sheer volume of data generated from genomic sequencing requires robust bioinformatics tools and expertise for analysis. The need for standardized protocols for data sharing and sequencing is crucial to ensure that scientists worldwide can access and interpret information consistently (Shu & McCauley, 2017). Collaborative initiatives like the Global Initiative on Sharing Avian Influenza Data (GISAID) have set a precedent for data-sharing frameworks, and similar models could be applied to MPXV and other emerging viruses (Harini *et al*., 2026). Another challenge lies in the interpretation of genomic data to predict phenotypic outcomes. While certain mutations can be linked to changes in virulence or transmissibility, not all genetic variations have clear implications. Functional studies are necessary to validate the impact of these mutations, adding a layer of complexity to genomic research (Zabidi *et al*., 2023). Moreover, the rapid pace of viral evolution can lead to the emergence of variants with altered characteristics, potentially undermining the effectiveness of current vaccines and therapeutics. Continuous global surveillance, backed by cooperative data-sharing and research, is essential to keep pace with these evolutionary dynamics and inform public health responses (Lansiaux *et al*., 2022).

The Role of Multi-Disciplinary Collaboration in Genomic Research

Addressing the challenge of MPXV requires collaboration across various scientific and medical disciplines. Genomic research benefits significantly from a convergence of virology, bioinformatics, immunology, and public health expertise. Virologists contribute knowledge on the structure and function of the virus, guiding genomic sequencing efforts and helping interpret findings (Malaka *et al*., 2025). Bioinformaticians play a crucial role in analyzing the vast amount of data generated from sequencing, identifying patterns, mutations, and evolutionary trends. Their algorithms and models can predict which genetic variations might impact the virus's behavior and potential resistance to therapeutics. Immunologists contribute by identifying which viral antigens could elicit strong immune responses, influencing vaccine design. Public health experts ensure that findings from genomic research are translated into actionable policies and response strategies that protect populations (Satapathy *et al*., 2025). Interdisciplinary collaboration also extends to partnerships between academic institutions, governmental health agencies, and private sector entities. Joint research initiatives accelerate the pace at which genomic insights can be applied to real-world solutions, such as vaccine and therapeutic development (Zhang *et al*. 2023). For instance, partnerships between biotech companies and universities have proven successful in rapidly advancing mRNA vaccine technology for COVID-19, a model that could be replicated for MPXV. Non-governmental organizations and international health bodies can provide critical funding and logistical support to expand genomic research in low-resource settings where MPXV is endemic (Ma *et al*., 2024). The collective effort of these multi-disciplinary teams enables a holistic approach to managing the virus, ensuring that advancements in genomic research translate into tangible benefits for global health (Zhang *et al*., 2024).

Summary and Future Directions

The future of MPXV research should focus on translating genomic surveillance into predictive and rapidly deployable countermeasures. Artificial intelligence (AI) and machine learning (ML) can integrate genomic, epidemiological, structural, and immunological datasets to identify mutation patterns, prioritize variants for functional validation, and predict changes that may affect transmission, immune recognition, or antiviral susceptibility. Such models could support evidence-based updating of vaccine antigen combinations and help prioritize experimental candidates before major changes become widespread (Najafi *et al*. 2022; Martínez-Fernández et al., 2023; Zhang *et al*., 2024; Iyyanar *et al*., 2025).

Rapid molecular diagnostics are another important priority. CRISPR-Cas-based assays, particularly approaches coupled with isothermal amplification, offer a potential route to sensitive, portable, and point-of-care MPXV detection, although assay robustness, target conservation, contamination control, and validation across clades must be resolved before broad clinical adoption (Chen *et al*., 2025). In parallel, pan-orthopoxvirus vaccine development should prioritize highly conserved genomic and antigenic regions shared across orthopoxviruses, with computational antigen selection followed by experimental immunogenicity and protection studies (Puagsopa *et al*., 2025). Long-term progress will also depend on equitable genomic surveillance capacity, standardized data sharing, and integration of laboratory, epidemiological, and computational evidence so that diagnostic, vaccine, and therapeutic strategies can be updated as MPXV evolves.

Conclusion

The genomic era has transformed the way infectious diseases are studied, offering unparalleled insight into the complex biology of viruses like MPXV. By dissecting the virus's genetic code, researchers can identify potential weaknesses that can be targeted by vaccines and therapeutics. The advancements in sequencing technology, from traditional Sanger sequencing to cutting-edge long-read platforms, have allowed for a detailed understanding of the MPXV genome, guiding efforts to track its evolution and predict its impact on public health. Challenges persist, including limited surveillance in endemic regions and the need for functional validation of genetic mutations. However, the lessons from past public health triumphs, such as the eradication of smallpox, offer valuable guidance. The future of combating MPXV lies in multi-disciplinary collaboration, global cooperation, and continued investment in genomic

research to pre-emptively address potential threats. As genomic tools and techniques evolve, so too will the ability to develop tailored, effective, and adaptive solutions that can safeguard against MPXV and other emerging zoonotic diseases.

Declaration of Interest Statements

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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