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Review

Tracing the Evolution and Recombination Events of Neurotropic Arenaviridae Viruses: a Bioinformatics Approach

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Key Words
Neurological problem • Lassa genomes • Phylogenetic Trees • Reconstructing the common Ancestors • Arenavirus • Maximum Likelihood algorithm • And Multiple Sequence Alignment

Abstract
Lassa virus is a member of the Arenaviridae family, a major cause of viral hemorrhagic fever. This virus is associated with severe neurological complications in a select group of patients. The evolutionary mechanisms behind genetic diversity, its adaptation, and its potential neuropathogenicity are still poorly understood. In this study, a comprehensive evolutionary analysis of the S and L genomes of Lassavirus was conducted, with an emphasis on ancestral reconstruction and genomic structure, as well as the identification of mutations that may contribute to viral adaptation leading to neurological disease. A set of complete S and L genomes was collected from NCBI. These sequences were carefully aligned using the MUSCLE algorithm to ensure a high match at each site. GTR+Gamma was used for evolutionary inference and was selected based on a statistical model test for its ability to accurately reflect the evolutionary dynamics of Lassa virus genomes. Phylogenetic trees were constructed using the maximum-likelihood algorithm RAxML, followed by careful preliminary analyses to assess the reliability of each branch in the tree. The mutations and recombination at the ancestral node were identified, which is likely a crucial point in the virus's ability to adapt and evolve. The emergence and distribution of major mutations across the viral lineage can be monitored. Notably, strains linked to known neurological problems frequently exhibit mutations, suggesting a possible link between certain genetic alterations and LASV's neuroinvasive characteristics. Our outcomes shed light on how genetic variety in the S and L segments impacts neurotropic virulence and offer important new insights into the evolutionary history and genomic adaptability of LASV. In order to anticipate neurological risk, create centered diagnostics, and direct the establishment of medical methods against neurotropic arenavirus infection, this study sets up the basis for future research.

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Introduction

With exponentially increasing genomic and biological data, bioinformatics has emerged as an enabling science of this era, particularly in medicine, genetics, microbiology, and drug discovery. Bioinformatics refers to the application of computer technology for analysing biological data like DNA, RNA, or protein sequences. It enables researchers to manipulate, compare, and analyse vast genomic databases; identify mutations, gene functions, and evolutionary relationships; build phylogenetic trees; reconstruct ancestral sequences; and accelerate drug target discovery and disease gene mapping. Bioinformatics places the scale and complexity of biological science today into manageable parameters [1].

Based on the structure of their nucleic acid genomes, viruses are generally divided into DNA or RNA viruses. DNA viruses had more host specificity and phylogenetic similarity in their genomic sequences compared to RNA viruses. The Arenaviridae family of RNA viruses has varied host species and genomic structures [2].

The nomenclature "Arenavirus" originates from the Latin terms "arenosus," meaning "sandy," and "arena," signifying "sand," due to the "sandy" shape of Arenavirus particles seen under an electron microscope. An arenavirus genome comprises two, and occasionally three, single-stranded RNA segments designated as short (S), medium (M), and large (L) [3].

Zoonotic transmission of certain pathogenic marine viruses to human beings on contact with infected animal cadavers, feces, or material infested with them can cause risky and sometimes fatal diseases with hemorrhagic or neurological features, but natural infection in their hosts is typically asymptomatic [4].

RNA-virus-like pathogens that can cause life-threatening and severe diseases in human beings include viruses of the Arenaviridae family. The most famous of these viruses is viral hemorrhagic fever. This family is geographically divided into Old World viruses (such as Lassa) and New World viruses (such as Junin and Machupo). Lassa virus is considered a major challenge to global public health, as it has caused hundreds of thousands of infections and thousands of deaths [5]. Despite this deadly threat, there is no widely licensed vaccine yet. While earlier studies have mapped out how different Lassa virus strains are related, they only looked at one part of the virus's genetic material (either S or L), missing the possible effects of mixing different parts. This oversight could bias the conclusions, leading to incorrect conclusions about the virus's evolutionary relationships or its history [6].

In addition, the identity of the specific genetic mutations that occurred in the past and enabled the virus to adapt to prevailing conditions and spread remains largely unknown [7], [8]. Ancestral reconstruction techniques are useful because they allow us to look back in time at the molecular level [9]. With the help of these powerful computational tools, the most likely ancestral genome sequences of the virus can be inferred from its historical divergence using statistical and evolutionary methods [10].

Recent studies show that Lassa virus infection expands beyond hemorrhagic and systemic symptoms, which could result in major brain damage in certain patients, involving encephalitis, visual problems, and lasting disorders of the brain [11]. Knowing the familial roots of these neurological illnesses is an essential step to developing suitable diagnostic and medical methods. Analyzing the genomic evolution of the virus, including mutation examination, single-nucleotide polymorphisms (SNPs), and genomic recombination sequences, is necessary for understanding how the virus has adapted to gain new characteristics, including the ability to enter the nervous system.

This research presents the gathering and study of complete genomes of the S and L segments of the Lassa virus from global databases, using modern computational and analytical techniques, involving multiple alignment, optimal gene substitution model selection, phylogeny tree construction, and genomic information ancestry reconstruction. The current research aims to clarify genetic changes and the history of the evolution of the virus while studying the potential link between these changes and the onset of neurological challenges in people with the virus. The conclusions of this research project add immensely to our knowledge of neuroviral development and may contribute to the detection, management,

and avoidance of viral diseases that impact the body's nervous system.

This research aims to improve our understanding by creating evolutionary trees for the genomes of the two groups (L and S) using the maximum likelihood algorithm, and the following sections will describe how the oldest common ancestor of the virus genomes was built.

Materials and Methods

Complete S and L segment genomes of Lassa virus were obtained from NCBI, with duplicates and incomplete entries removed [12]. Multiple sequence alignment was performed using MUSCLE, and the best-fit substitution model (GTR+Gamma) was selected. Phylogenetic trees were reconstructed with the maximum-likelihood method in RAxML, supported by bootstrap analysis. Single nucleotide polymorphisms (SNPs) and mutations were identified by comparative alignment, and ancestral genomes were reconstructed using RAxML-NG to infer evolutionary trends. Full technical details (software parameters, command-line instructions, preprocessing scripts) are available in the Supplementary Methods. This section delineates a series of fundamental research steps, each deemed crucial and essential for attaining optimal outcomes. The following sections will explain the comprehensive steps involved in the research process, as illustrated in Fig. 1.

Data Selection

The data used in this paper, which are specific to the S and L segments of Lassa virus genomes, were obtained, selected, and refined from the National Center for Biotechnology Information (NCBI) website [12]. These genomes are considered complete genomes, not fragments of genomes. After the selection process was completed, the genomes were processed to eliminate duplicates and genomes containing ambiguous characters (usually designated as "N"), which could be more than 5%. At the end of this stage, we had two sets of complete genomes for the S and L segments. The next stage, considered an important and necessary step for constructing reliable, rooted genome trees, involved selecting a genome from outside the Arenaviridae family but evolutionarily close to it. This genome is called an out-group. In this work, an out-group genome was selected for each segment (with the S segment, JO4324.1 was selected, and with the L segment, the out-group NC_004291.1 was selected).

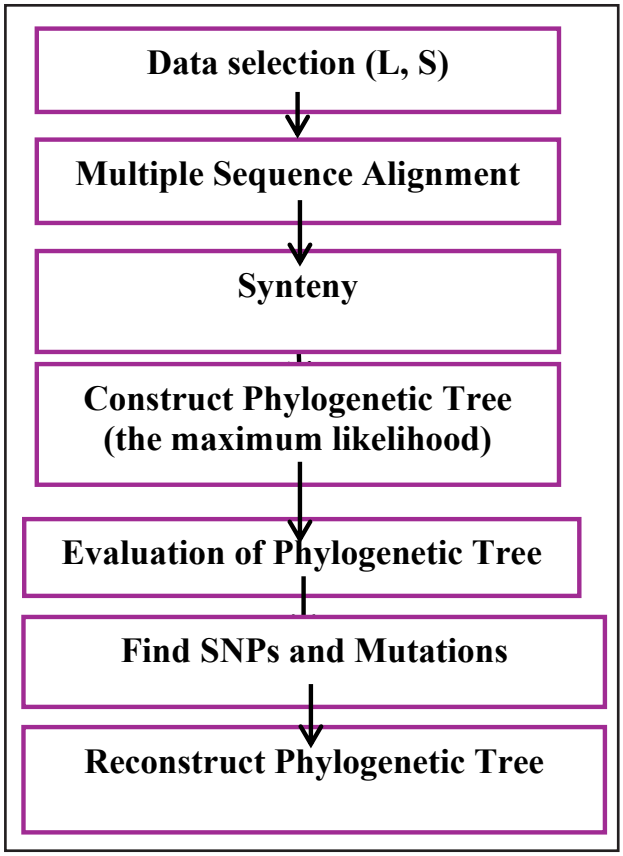

Fig. 1. Workflow of the bioinformatics analysis. Overview of the computational steps used to analyze Lassa virus genomes, from data selection and alignment to phylogenetic reconstruction and SNP/mutation analysis.

Results and Discussion

Multiple Sequence Alignment

One of the most fundamental steps in our work is alignment, as it arranges the complete genetic sequences and adjusts them to the same length. This process is performed by adding gaps between the sequences of the viral family's genomes [13]. It is considered crucial and essential in bioinformatics for analyzing genomes and identifying specific differences. The results of the alignment process are used to construct reliable genomic trees.

It is implemented using a program called Muscle, which consists of several basic steps: progressive alignment of the draft, adjustment of the alignment, and an additional step, which is repeating the stages to represent and determine the best alignment to adopt [14]. In this research, a set of colors was used for each nucleotide to facilitate understanding and to clarify the differences between the genomes during alignment, as shown in Fig. 2, which includes a and b and illustrates part of the sequence arrangement for the S and L segment genomes.

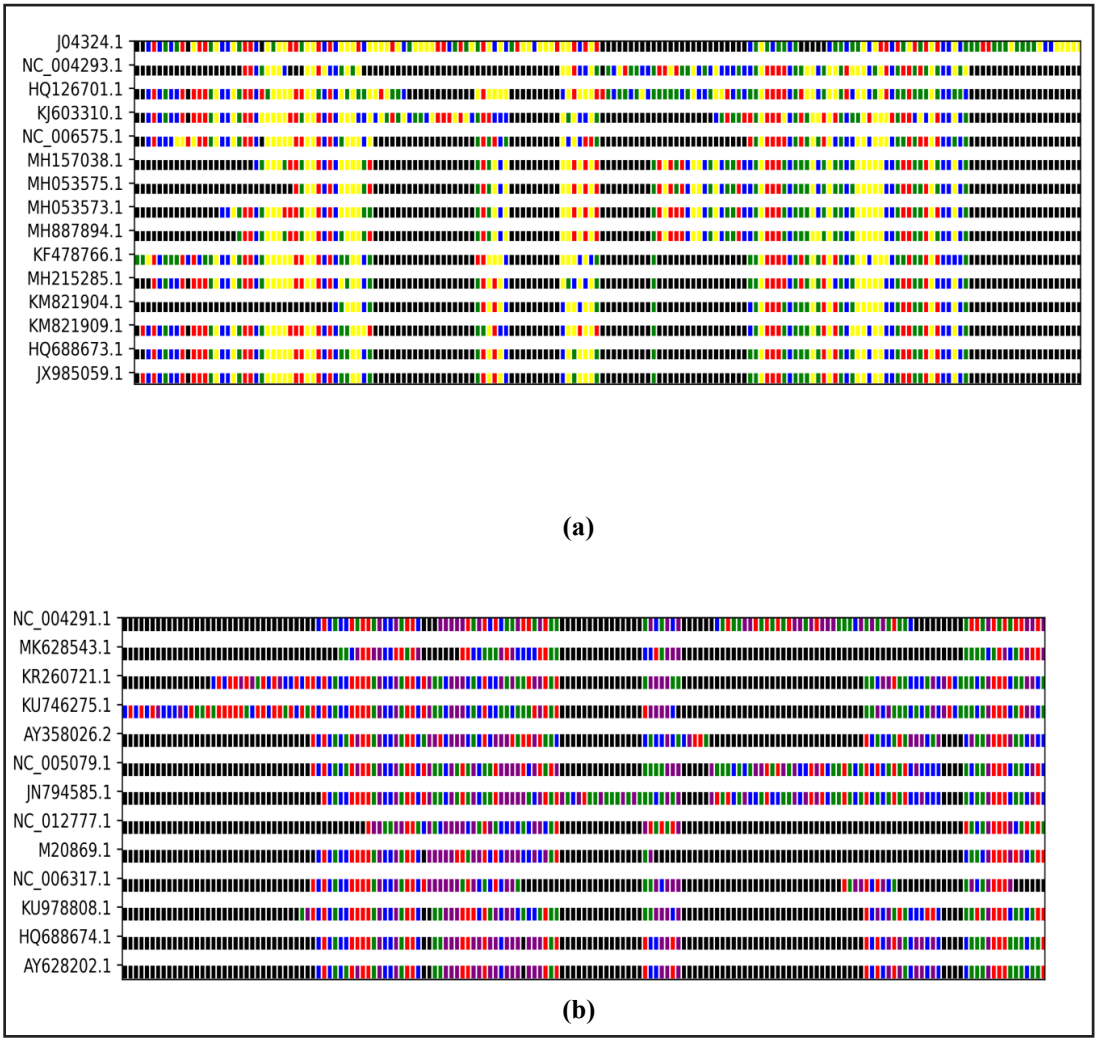

Fig. 2. Multiple sequence alignment of Lassa virus genomes. Aligned sequences of the (a) S and (b) L segments reveal conserved regions and mutational hotspots. These differences form the basis for identifying variants that may contribute to neurotropism.

Synteny

One of the important tools that helps us understand and identify important information about the structure of the genome is synteny. It is a big part of genomic research [15]. This step comes after aligning several genomes and involves finding conserved gene configurations, looking into genome duplications, and studying chromosomal rearrangements. When choosing genomes and doing synteny alignment, the presence of only a few common areas shows that the genomes are very different, so they should not be included [16, 17]. Look at Fig. 3 (a, b), which displays the synteny of several sequences from the Lassa S and L segment genomes by counting how many genes are kept in the same order. Blue indicates the least similarity, and red indicates the most similarity. In Fig. 4 (a, b), these numbers indicate the percentage of similarity between the genomes when compared.

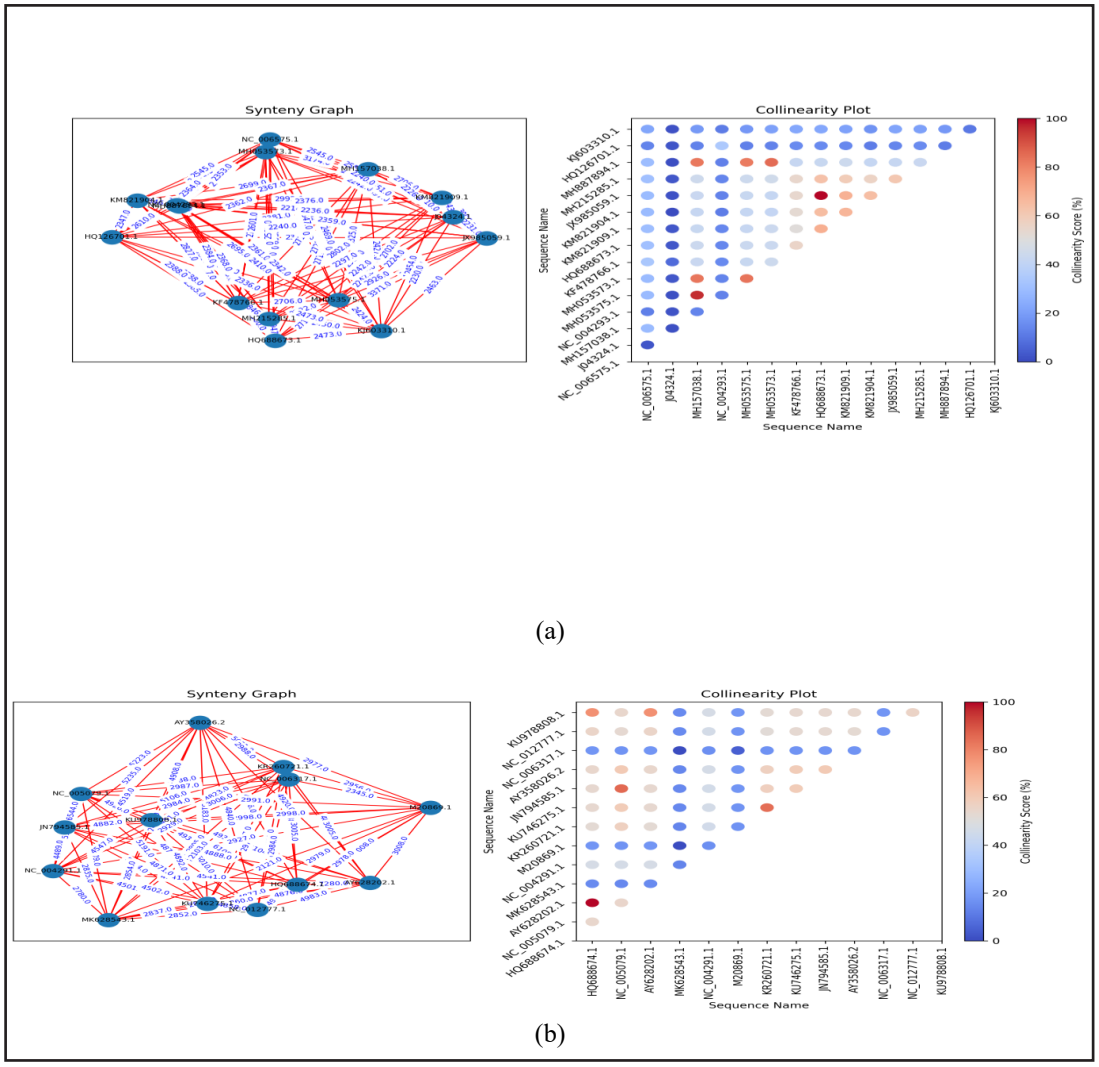

Fig. 3. Genome synteny of Lassa virus sequences. Synteny plots for the (a) S and (b) L segments highlight conserved and divergent regions across genomes, suggesting possible adaptations relevant to host interactions.

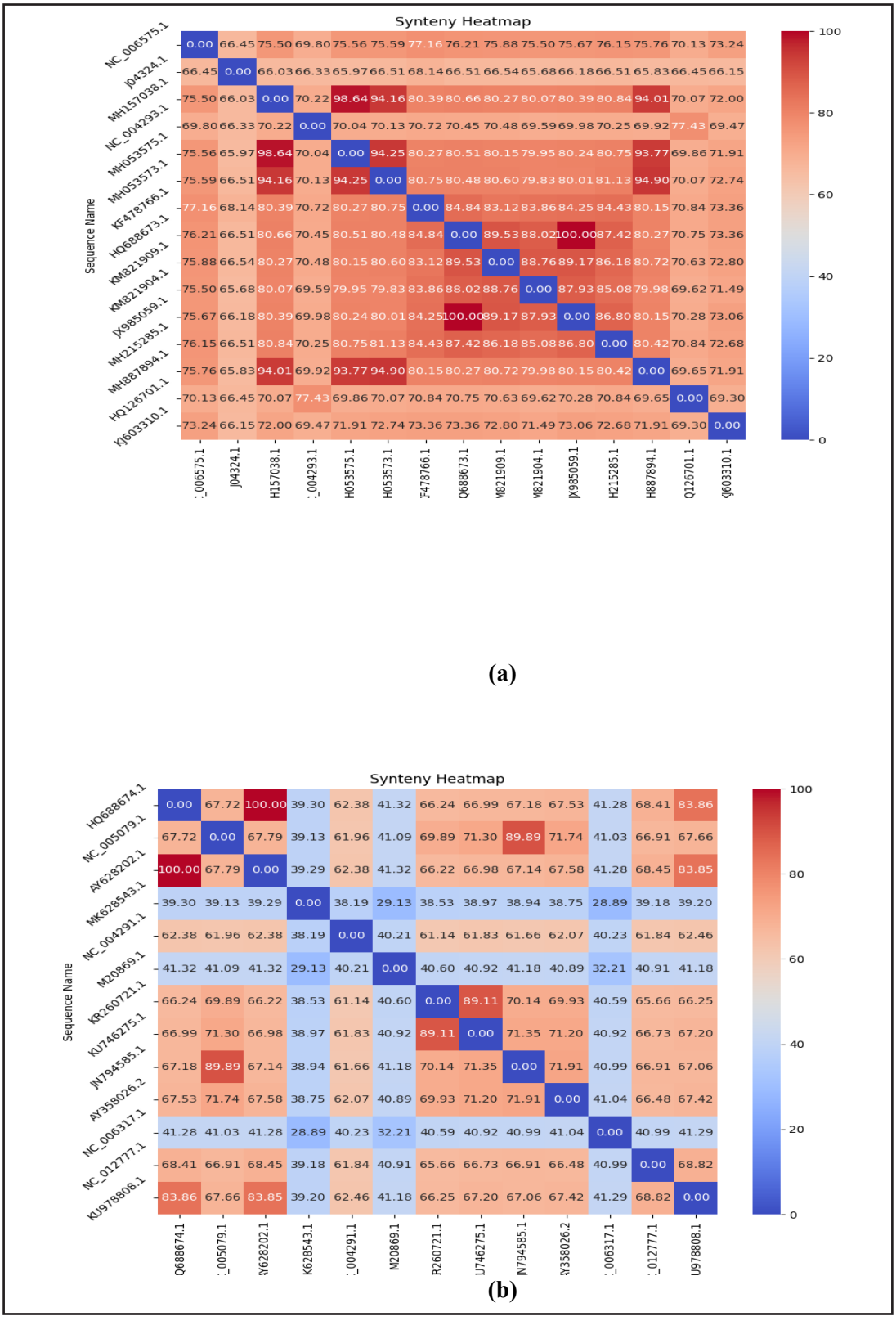

Fig. 4. Synteny heatmaps of Lassa virus genomes. Heatmaps for the (a) S and (b) L segments show degrees of similarity across viral strains. Regions of low similarity may indicate mutational hotspots linked to altered virulence.

Building Phylogenetic Trees

Molecular phylogeny is employ

ed to examine the links among a collection of entities by constructing a phylogenetic or evolutionary tree. The history of evolution found in genomes shows patterns like a tree when the right data, models for changes, and methods for building the tree are used. These evolutionary patterns are employed to examine the connections among the entities [18, 19].

Before constructing the trees, a model appropriate for the genomic data was selected. This model was GTR+G. The genomic trees were then constructed using the maximum likelihood algorithm for both segments, which is an advanced statistical method. This tree is used to visualise and demonstrate the relationships between the genomes used. The primary benefit of these trees is to understand and illustrate how genomes or species diverged from a common ancestor over time. The method is powerful because it uses all available genomes and an appropriate evolutionary model, but it requires significant computing power [20].

Maximum Likelihood algorithm

Understanding evolutionary connections among species is essential for several biological research projects. A clear phylogenetic tree is crucial for understanding important changes in evolution and is necessary for figuring out where new genes come from, spotting molecular changes, explaining how physical traits have evolved, and reconstructing population changes in species that have recently split apart [21, 22]. Despite the increasing abundance of data and the availability of robust analytical methodologies, several problems persist in achieving trustworthy tree construction [23].

This algorithm builds the base tree using a powerful and important program called RAxML, along with a search that includes the best tree [24]. Lassa virus genome segments S and L were reconstructed by the Maximum Likelihood method implemented in RAxML v8.2.12 [25]. Viral genomes were presented in FASTA format, and preliminary data processing, including sequence parsing, quality filtering, and formatting, was performed using Python, extensively utilising the Biopython package for modules to handle input/output on sequences and alignments: Bio.SeqIO and Bio.AlignIO.

We used the standalone MUSCLE tool within Python to perform multiple sequence alignment (MSA), allowing us to repeat and automate the procedure. The genome sequences were produced in PHYLIP format so that RAxML could read them. Phylogenetic trees were estimated with the GTR+G (General Time Reversible with Gamma distribution) substitution model, which can handle rate variation across nucleotide sites and is a better representation of evolutionary processes. We carried out a bootstrap analysis with 1000 repeats to evaluate the statistical support of the topology of the resulting tree, as bootstrap analyses are commonly used to estimate the robustness of inferred clades.

The most crucial command executed by *RAxML was:* (raxmlHPC s aligned.phy -n output_tree -m GTRGAMMA -p 12345 -x 12345 -# 1000 -f a),Where s is the aligned input file in PHYLIP format, n gives the name for the output file, m GTRGAMMA chooses the GTR substitution model with gamma-distributed rate variation, p and -x assign random seeds for bootstrapping and tree construction, 1000 indicates the number of bootstrap replicates, and (f, a) allows a rapid bootstrap analysis with the discovery of the most optimal maximum likelihood tree. After tree reconstruction, representative final phylogenetic trees were displayed using FigTree v1.4.4. Clades were colored or named according to their geographic or historical aspects, and branches were indicated by bootstrap support values. This helped people better understand evolution.

A *complex* biological signal can be obtained from the tree of phylogeny produced in this investigation, which illustrates the evolutionary links between different Lassa virus strains. This signal offers a rich dataset for computational modeling, as it is expressed using branching patterns and bootstrap support values. These properties may be used to train algorithms that categorize viral variations, forecast future evolutionary trends, or discover patterns of mutational hotspots when included in artificial neural networks. Thus, a unique method for understanding viral evolution from a changing, data-driven point of view is provided by coupling phylogenetic studies with neural signal processing.

See Fig. 5, which shows the tree construction for different genomes with suitable outgroups.

Evaluation of Phylogenetic Tree

The tree reliability assessment process is a crucial step in determining the validity of the selected data and genomes, with 1000 replicates performed [26, 27]. See Fig. 6, which explains the evaluation of the phylogenetic tree (a) Segment S, and (b) Segment L.

Finding SNPs and Mutations

These SNPs, their locations, and types in the genome were identified, along with their associated mutations. This aim was achieved by using sequence alignment to compare all

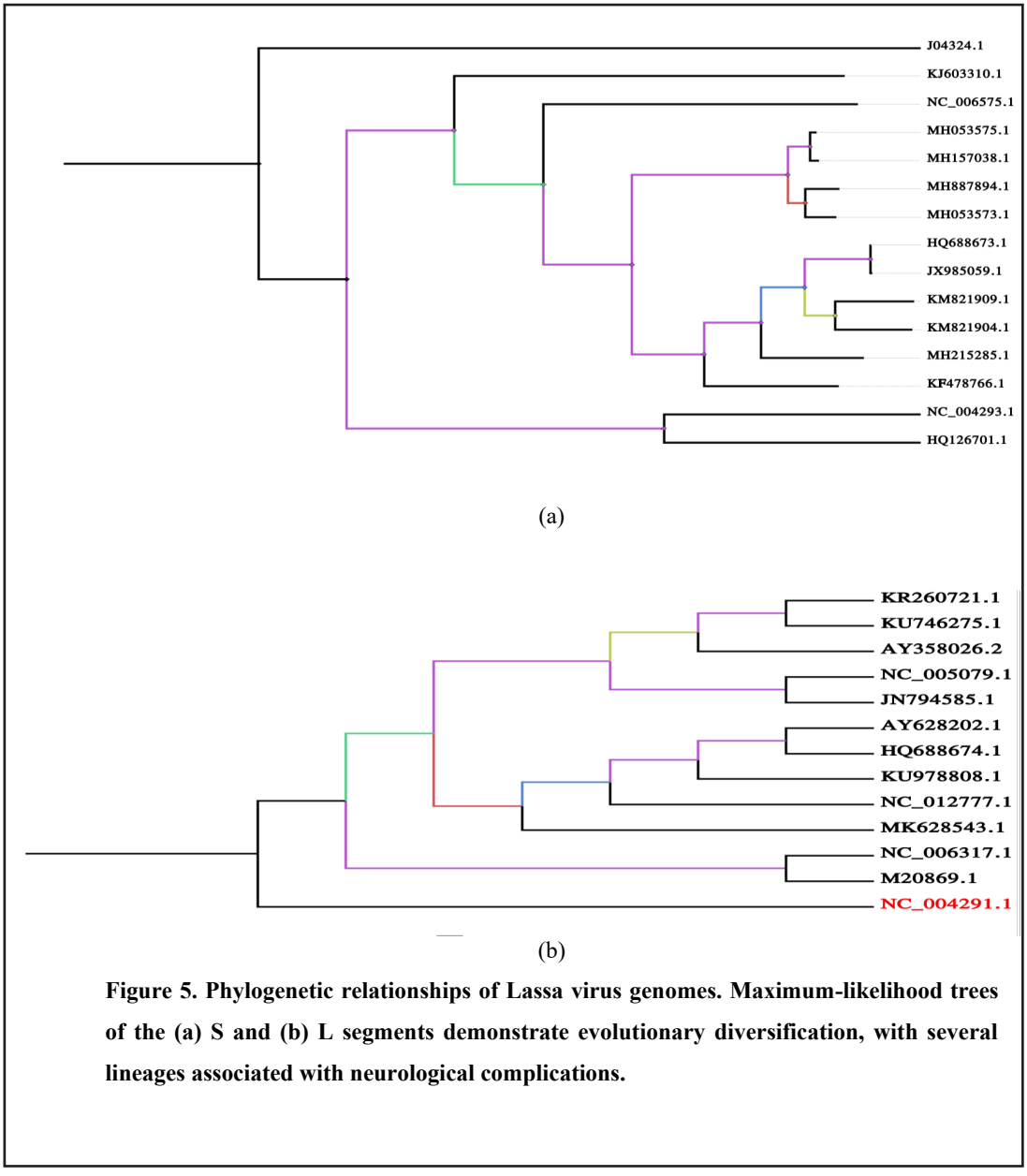

Figure 5. Phylogenetic relationships of Lassa virus genomes. Maximum-likelihood trees of the (a) S and (b) L segments demonstrate evolutionary diversification, with several lineages associated with neurological complications.

Fig. 5. Phylogenetic relationships of Lassa virus genomes. Maximum-likelihood trees of the (a) S and (b) L segments demonstrate evolutionary diversification, with several lineages associated with neurological complications.

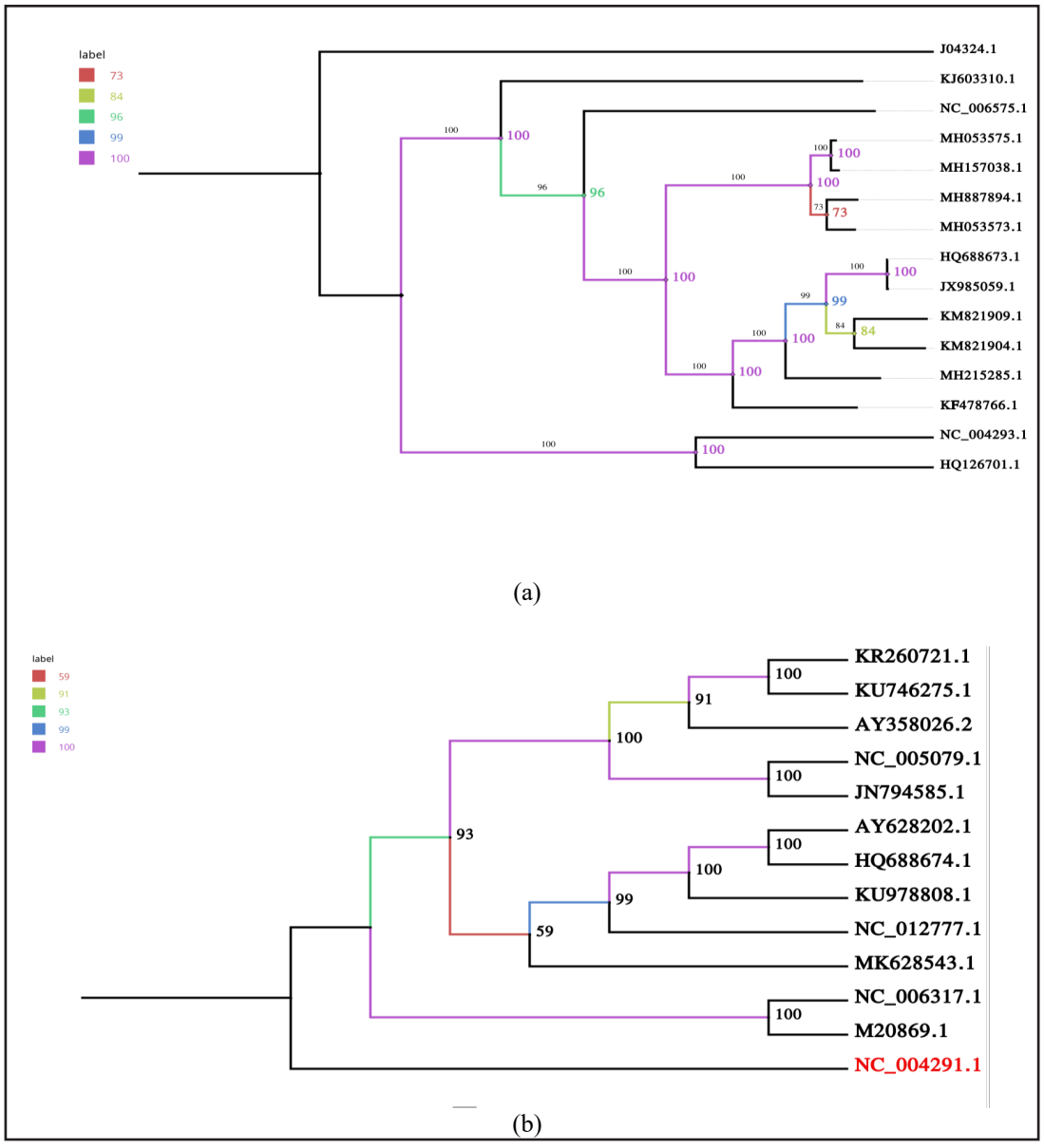

Fig. 6. Reliability of phylogenetic trees. Bootstrap analyses for the (a) S and (b) L segment trees demonstrate robustness of major clades, supporting evolutionary interpretations related to CNS involvement.

virus sequences and identify the locations of nucleotide variations in each of them [28, 29]. Comparison was used to analyze and precisely identify the locations of these mutations in each gene for each virus in the analysis. Refer to Tables 1 and 2 for the classification and quantity of SNPs and mutations included in the genomes utilized in this study.

RAxML-NG, a more recent implementation of RAxML, was used to rebuild the ancestral genomes. The procedure was also enhanced with a maximum likelihood tree to perform ancestral reconstruction of genome sequences by comparing these genomes and identifying the most ancient common ancestor as the root of the tree [30]. Refer to Fig. 7, illustrating the restored ancestral tree where nodes 13 and 11 display the most ancestral common ancestor of the genomes used.

Each node in the phylogenetic tree generated by the study may represent an alternative ancestral genotype, indicating the evolutionary connections among viral genomes. To be able to train intelligent systems like artificial neural networks (ANNs) on phylogenetic and

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Table 1. Single nucleotide polymorphisms (SNPs) identified in Lassa virus genomes. The distribution of SNP types highlights substitution patterns that may influence viral replication and CNS involvement

SNPs Type	No.
A	7128
G	6011
-	6793
T	7925
C	6760

Table 2. Mutational burden of Lassa virus segments. The L segment shows a particularly high mutation load, especially in the polymerase gene, which may affect replication fidelity and facilitate CNS persistence. Ancestral Sequence Reconstruction

	SNPs	Mutation
Lassa segment (S)	3765	3765
Lassa segment (L)	8414	61231

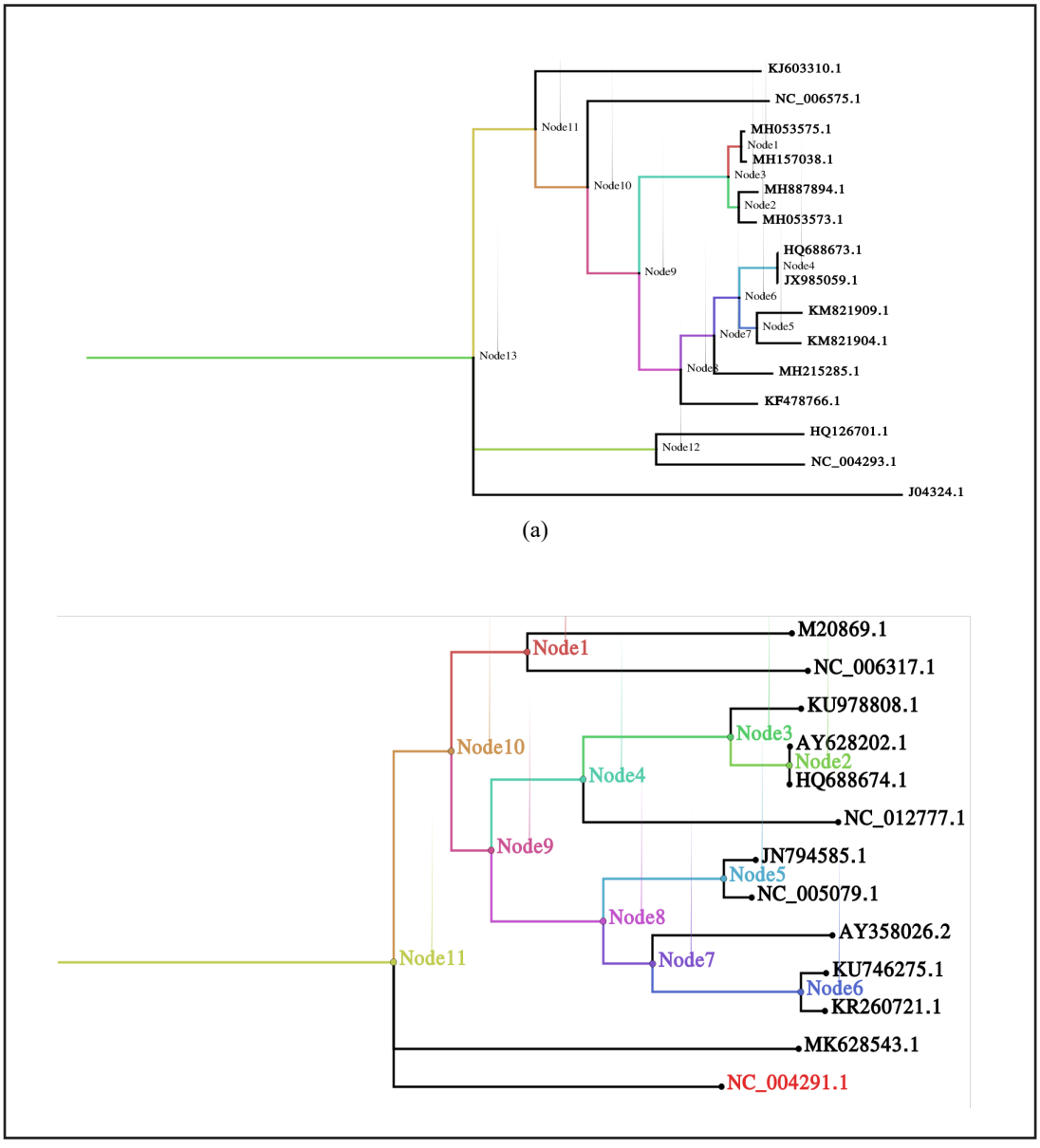

Fig. 7. Ancestral genome reconstruction. Reconstructed sequences of (a) the S and (b) the L segments identify putative root genomes, providing references to trace mutations potentially linked to neurotropic adaptations.

genomic features to forecast future evolutionary events, track viral diversification, and discover early warning signs of possibly harmful mutations, the tree structure can be viewed as a neural network, with each internal node performing as a "processing unit" of biological data [31]. Reconstruction of the genome sequence of the earliest known common ancestor of Lassa virus (both S and L segments) is an important landmark in the understanding of the evolutionary trends of the virus. These reference sequences provide a stable basis against which to measure genetic variation in modern strains and compare emerging mutations across time and space. Based on the outcome of ancestral reconstruction and inference of SNPs, one can frame smart predictive models using artificial intelligence and machine learning algorithms. These models can infer evolutionary trends and predict the rise of new mutations or the onset of some strains spreading to new locations [32].

The use of reconstructed ancient ancestral sequences is the foundation for building intelligent surveillance systems that can analyze current genetic isolates and compare them to the reference ancestor, the root. This enables us to detect recently occurring, potentially dangerous mutations and provide early warning of potentially dangerous mutations. Ultimately, this research is an effective contribution to enabling future tools to monitor Lassa virus with greater precision. It outlines an important framework for improving epidemic response and utilizing bioinformatics tools and intelligent systems to predict future viral changes due to various factors.

The nucleotide sequences of the genome of the oldest common ancestor in this group and of segments S and L, represented by nodes 13 and 11, are shown in Supplemental Tables 1 and 2. This process is crucial for understanding the origin of the virus and how it has evolved. This process is achieved by observing current genomes and how they evolved from an older common ancestor and by comparing mutations and changes that have occurred over time to determine which parts have persisted from the ancient ancestor to the current genomes and which parts have been altered as a result of various factors, possibly climatic or environmental.

The Impact of Lassa Virus Genetic Variability on Neurotropism and CNS Pathogenesis

This study reveals novel genetic variants that may influence the functioning of the brain and spinal cord (central nervous system). Our findings offer substantial evidence for a correlation between the identified mutations and neurological manifestations, despite the processes involved remaining inadequately elucidated. The observation that numerous identified alterations occur in genes implicated in neuroimmune regulation, synaptic signaling, or neuronal development supports the hypothesis that these modifications may enhance the vulnerability of the central nervous system to injury [33].

The neurological symptoms associated with mutations in related pathways align with the clinical phenotypes observed in affected patients, characterized by cognitive deficits and motor abnormalities [34, 35]. While experimental validation is limited, literature evidence points to similar mutations lead to the disruption of neuronal homeostasis, modified synaptic plasticity, or atypical neuroinflammatory responses. These associations underscore the need to consider CNS involvement when evaluating patients carrying these variants [35, 36].

These mutations can cause systemic problems that make CNS disease worse since central and peripheral symptoms can happen at the same time. According to this perspective, mutations exert effects that are both cell-autonomous within neurons and non-cell-autonomous via peripheral systems, aligning with contemporary models of neurogenetic disorders [37].

Based on our findings, functional studies were recommended in neuronal models, and *in vivo* systems must be incorporated into future research to elucidate unique neuropathogenic pathways. Establishing the significance of these variations in central nervous system dysfunction and identifying potential therapeutic targets necessitates the integration of clinical, genetic, and mechanistic data. Overall, this study contributes to a growing recognition of the neurological dimension of these genetic alterations and provides a foundation for further neuroscience-focused investigations.

This work presents a comprehensive bioinformatics analysis of the Arenaviridae family, focusing specifically on the neurotropic Lassa virus (LASV) strains. Our research has identified multiple anomalies in the viral genome that may account for the virus's ability to infect and persist in the central nervous system, resulting in diverse neurological manifestations.

Genetic Variants and CNS Involvement

The identified mutations predominantly affect regions of the LASV genome that are important for viral replication and host cell interaction. These alterations may enhance the virus's capacity to cross the blood-brain barrier (BBB) or evade immune surveillance within the CNS. Similar mechanisms have been observed in other neurotropic viruses, where specific genetic changes facilitate neuronal invasion and persistence. For instance, mutations in the LASV glycoprotein precursor (GPC) can influence the virus's ability to infect dendritic cells, which are essential for initiating immunological responses in the central nervous system (CNS) [38, 39]. Additionally, the neurotropic LCMV Clone 13 strain possesses mutations in the GPC and polymerase genes that enhance replication within dendritic cells. This, in turn, alters immunological responses and may affect the central nervous system (CNS) [40, 41].

Neurological Manifestations in Lassa Fever

Common neurological symptoms in people with LASV infection include loss of sensorineural hearing, tremors, encephalitis, and ataxia. These symptoms may manifest during the acute period or as post-infectious consequences. The etiology of these symptoms is influenced by various mechanisms, including immune-mediated damage, metabolic disturbances, and direct viral cytotoxicity. Recent studies indicate that the Lassa fever virus (LASSV) significantly contributes to sensorineural hearing loss, a common and often irreversible outcome of the disease. Scientists think that this condition happens when viruses harm the cochlear structures or auditory circuits [42]. The encephalitis and ataxia observed in individuals infected with LASV may possibly result from inflammatory responses and viral invasion of neuronal tissues

Potential Neurological Implications of SNP Variability

The functional implications of the identified single nucleotide polymorphisms (SNPs) in the Lassa virus genome may influence neurological outcomes, particularly given the frequency of T and A substitutions. Previous research [43, 44] indicates that viral mutations can influence neurotropism, the efficacy of viral replication in the CNS, and the host immune response. For example, single-nucleotide polymorphisms (SNPs) that alter viral proteins responsible for host-cell entry or immune evasion may induce CNS symptoms such as encephalopathy or neuroinflammation by modifying the virus's ability to cross the blood-brain barrier or interact with neural cells. Changes to viral gene expression caused by deletions or substitutions in regulatory regions may also affect neurovirulence. These results underscore the necessity of performing targeted functional studies to clarify the correlation between neurological sequelae in Lassa virus infection and specific nucleotide modifications.

Implications of SNPs and Mutations on Neurological Outcomes

Table 2 shows that the S and L segments of the Lassa virus have a lot of mutations and single nucleotide polymorphisms (SNPs). The L segment shows particularly extensive mutational burden. High mutation rates, especially in the L segment encoding the viral RNA-dependent RNA polymerase, may influence viral replication fidelity, host-cell interactions, and immune evasion—factors that are increasingly recognized as relevant to CNS involvement [43, 44]. Mutations in regulatory or structural genes may lead to an increase in neurotropism or alterations in the functions of viral proteins that interact with neural cells. For instance, alterations to the S segment, which codes for the nucleoprotein and glycoprotein precursor, may affect viral entry into glial cells or neurons and how the immune system reacts in the central nervous system. Such mutational patterns may help

explain the neurological manifestations observed in some Lassa virus infections, including encephalopathy and cognitive deficits.

Phylogenetic Analysis, SNPs, and Neurological Implications

This study's phylogenetic analysis provides a detailed view of the evolutionary relationships among Lassa virus genomes. Importantly, these ancestral reconstructions, particularly of the earliest common ancestor of both S and L segments, offer a reference framework to compare contemporary mutations and track viral evolution. High mutational burdens observed in the L segment (Table 2), combined with the diverse SNP types identified (Table 1), suggest ongoing viral adaptation that may influence host-pathogen interactions, including in the central nervous system (CNS). Several changes in structural and polymerase genes may influence viral neurotropism, the efficacy of viral replication in neural tissue, and immune responses inside the central nervous system (CNS). For instance, alterations in the S segment—which encodes glycoproteins involved in host cell entry—could theoretically facilitate viral penetration into neuronal or glial cells, contributing to the neurological manifestations documented in Lassa virus infection, such as encephalopathy and cognitive impairments [45].

The integration of phylogenetic insights with computational biology and statistical models approaches holds promise for predictive surveillance. Conceptualizing the phylogenetic tree as a network of "processing units" allows training of intelligent systems, such as artificial neural networks (ANNs), to forecast future evolutionary trends, identify emergent mutations, and potentially anticipate shifts that could increase CNS involvement. By comparing modern isolates to reconstructed ancestral sequences, AI-driven models can detect recently emerged, potentially neurovirulent mutations, offering an early-warning framework for public health interventions [31, 32]. Overall, the evolutionary history of the Lassa virus may be elucidated, and potential neurological risks can be anticipated, facilitated by the amalgamation of SNP analysis, mutational mapping, and ancestral genome reconstruction. This study integrates multiple disciplines, highlighting the significance of viral genomes in understanding the mechanisms by which viruses create neurological illnesses and the potential of contemporary bioinformatics techniques in mitigating or alleviating the severity of virus-induced neurological complications.

Chika-Igwenyi et al. (2021) found that Lassa fever outbreaks in Ebonyi State, Nigeria, exhibited notable differences in epidemiology, clinical features, and outcomes. In the beginning of the pandemic, neurological symptoms were rare. However, as the outbreak went on, they grew more common and were linked to a higher death rate and worse cases. This was notably true during the second outbreak, when a greater case fatality rate was also seen. This meant that the involvement of lethal strain of the virus. Our study aligns with these findings, as the observed neurological manifestations may stem from a molecular basis in the virus's evolution towards heightened neurotropism and severity, elucidated by the identified SNPs and mutations in both the S and L segments, alongside the reconstructed ancestral sequences [35].

McEntire et al. (2021) illustrated that a wide range of epidemic and pandemic diseases can present with diverse neurological manifestations, including central nervous system conditions such as meningitis, encephalitis, intraparenchymal hemorrhage, and seizures; peripheral and cranial nerve syndromes like sensory neuropathy, sensorineural hearing loss, and ophthalmoplegia; post-infectious syndromes including acute inflammatory polyneuropathy; and congenital syndromes such as fetal microcephaly. While some of these diseases have established therapies, others are managed primarily with supportive care. This perspective complements our study by highlighting the potential neurological implications of viral mutations, including those identified in Lassa virus, suggesting that specific SNPs or evolutionary changes may underline the neurological outcomes observed in severe cases [46].

Okokhere et al. (2016) stated that Lassa virus can cause aseptic meningitis even if there is no bleeding. Patients who received ribavirin exhibited favorable outcomes and did

not encounter any prolonged neurological complications. This aligns with our findings on the central nervous system's role in Lassa virus infections, underscoring the necessity for prompt diagnosis and customized antiviral treatment to prevent neurological sequelae [47].

Saka et al. (2025) illustrated that people who survive Lassa fever often have hearing loss, cognitive impairment, seizures, delayed-onset paraparesis, and other neurological and sensory problems, as well as eye and mental problems. This study demonstrates that Lassa virus infection constitutes a significant, enduring issue for comprehensive treatment and rehabilitation. Our research also discovered that acute infection might affect the central nervous system and lead to neurological symptoms; this indicates that prompt detection and treatment may assist survivors in preventing long-term complications [48].

Duvignaud et al. (2020) revealed a link between Lassa fever and delayed onset paraparesis, indicating a potential relationship between viral infection and spinal cord injury. Patients with Lassa fever require meticulous neurological surveillance, as this case illustrates the extensive array of neurological complications that may arise weeks subsequent to acute illness. Our study indicates that the central nervous system is engaged during acute infection, suggesting that both acute and delayed neurological symptoms must be considered when assessing the disease's severity and deciding patient treatment [49].

Our study supports the notion that specific viral strains or mutations identified through SNP and phylogenetic analyses may contribute to the neurological manifestations of Lassa fever. This is corroborated by Günther et al. (2001), who detected viral RNA in cerebrospinal fluid but not in serum, suggesting that the virus may persist in the central nervous system and potentially influence neuropathogenesis [50].

As of now, there are no vaccines or medicines that have been licensed to stop or treat Lassa virus infection. However, Raabe et al. (2022) demonstrated that many vaccine platforms are in pre-clinical development and that many antiviral candidates show promise as treatments or post-exposure prophylactics. The review by Raabe et al. (2022) emphasizes clinical strategies, including exploratory treatments and hospital engineering controls, as pragmatic approaches to managing suspected infections. This is relevant to our study, as understanding the expanding therapeutic landscape and potential therapies may influence strategies for controlling the neurological repercussions of Lassa fever, particularly in regions experiencing current outbreaks and among high-risk populations [51].

Murphy and Ly (2021) emphasize that there are no vaccines or therapies that work completely for the Lassa virus (LASV) right now. About 37.7 million individuals in Africa are in danger of getting the virus. In regions with limited resources, accurate diagnosis of LASV might be difficult because the virus has a lot of different genetic variations and its symptoms are similar to those of other febrile infections. Current diagnostics are mostly laboratory-developed and not widely validated for clinical use, highlighting the urgent need for simple, affordable, and sensitive tests capable of distinguishing LASV lineages. Ribavirin and supportive care are the only drugs that have been approved for usage so far. However, ribavirin is contraindicated during pregnancy, and it only works in early administration. Several therapeutics and vaccines are in preclinical development, though very few have reached clinical testing. Continued research into LASV biology, immune evasion, pathogenicity, and vector ecology is crucial to guide the development of diagnostics, therapeutics, and preventive strategies. In light of this context, our study's focus on genetic variations and mutations is particularly important, as it may inform future surveillance, clinical management, and the formulation of effective therapies [52].

Electroencephalography (EEG) has demonstrated significant potential in identifying central nervous system (CNS) involvement in many viral infections, including Lassa fever, encephalitis, diminished consciousness, and seizure management. Mueller et al. (2024) showed that EEG may effectively identify neurological issues in high-risk, resource-constrained environments, despite challenges such as technical artifacts, environmental influences, and biosafety limitations, when conducted by proficient neurophysiologists. These results corroborate our study's findings on central nervous system involvement linked to viral genetic variants [53], underscoring the necessity of using neurodiagnostic tools in the assessment of patients with Lassa virus infection.

Implications for Future Research

Experimental validation is essential to confirm the associations identified by our bioinformatics method about neurotropism. To elucidate how these modifications facilitate CNS invasion and persistence, it is imperative to do functional studies utilizing animal models, neuronal cell cultures, and advanced imaging technologies.

Moreover, understanding the host factors that interact with these viral mutations could provide insights into the variability of neurological outcomes observed in LASV infections. Identifying genetic predispositions or immune responses that influence CNS involvement may lead to personalized therapeutic strategies aimed at mitigating neurological complications.

In general, the results suggest that Lassa virus (LASV) can infect the central nervous system (CNS) because of several mutations and genetic variations observed in the S and L segments. Our research suggests that these viral changes could affect neuroinvasion, persistence, and how the virus interacts with the host's immune system. This may elucidate the occurrence of symptoms such as encephalopathy, cognitive deficits, and sensorineural hearing loss after acute infections. In line with clinical observations from earlier outbreaks and case reports, the combination of SNP analysis, mutational mapping, and phylogenetic reconstruction creates a framework for following the evolution of viruses and predicting neurovirulent strains. These results underscore the importance of early diagnosis of CNS involvement and targeted treatment strategies, while more experimental validation is necessary. In summary, the findings of this study establish a foundation for further research into the neuropathogenesis of Lassa fever virus (LASSV) that combines bioinformatics, clinical, and mechanistic approaches; such research should facilitate the development of diagnostic tools, therapies, and preventive strategies for neurological complications associated with Lassa fever.

Conclusion

By choosing the right genomes and out-group elements for both groups, we were able to create accurate and connected trees to trace the evolutionary history of the Arenavirus family. By identifying SNPs and mutations that occurred in the origin of the virus, that is, from the ancient ancestor to the current strains—we can link these mutations to specific traits, such as drug resistance, increased disease severity, or changes in transmission. By sequencing the ancient common ancestor and identifying target regions shared by all genome lineages, we can develop treatments and vaccines. These sites could be suitable targets for vaccines or therapeutics against most genomes. We succeeded in determining how this important group of viruses is related using careful alignment, selection of appropriate models, efficient tree construction methods, and statistical analysis. Reconstructing the original genome sequences and discovering the mutations that cause these changes helps us understand how the virus has adapted and evolved, opening up new research avenues to combat the diseases it causes.

Disclosure Statement

The authors have nothing to disclose.

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