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STRUCTURE AND GENOMIC ORGANIZATION OF HUMAN RESPIRATORY SYNCYTIAL VIRUS (HRSV)

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ABSTRACT

The COVID-19 pandemic has resulted in the implementation of strict mitigation measures that have impacted the transmission dynamics of Human Respiratory Syncytial Virus (HRSV). The measures also have the potential to influence the evolutionary patterns of the virus. In this study, we conducted a comprehensive analysis comparing genomic variations and evolving characteristics of its neutralizing antigens, specifically F and G proteins, before and during the COVID-19 pandemic. Our findings showed that both HRSV A and B exhibited an overall chronological evolutionary pattern. For the sequences obtained during the pandemic period (2019–2022), we observed that the HRSV A distributed in A23 genotype, but formed into three subclusters; whereas the HRSV B sequences were relatively concentrated within genotype B6. Additionally, multiple positively selected sites were detected on F and G proteins but none were located at neutralizing antigenic sites of the F protein. Notably, amino acids within antigenic site III, IV, and V of F protein remained strictly conserved, while some substitutions occurred over time on antigenic site Ø, I, II and VIII; substitution S389P on antigenic site I of HRSV B occurred during the pandemic period with nearly 50% frequency. However, further analysis revealed no substitutions have altered the structural conformations of the antigenic sites, the vial antigenicity has not been changed. We inferred that the intensive public health interventions during the COVID-19 pandemic did not affect the evolutionary mode of HRSV.

Key words : Human respiratory Syncytial Virus (HRSV) , COVID-19

INTRODUCTION

Human respiratory Syncytial Virus (HRSV) is a leading cause of acute lower respiratory tract infections in young children and poses a major risk to elderly individuals, imposing a substantial burden on healthcare systems worldwide (Shi et al., 2020; Li et al., 2022). Although HRSV infection can manifest as mild upper respiratory tract illness that typically resolves within 7–10 days without complications, severe lower respiratory tract infections such as bronchiolitis or pneumonia may occur. Infants and individuals with underlying medical conditions or weakened immune systems are particularly vulnerable, which can potentially result in mortality (Falsey and Walsh, 2000; Perk and Ozdil, 2018).

HRSV is a single-stranded, negative sense RNA, enveloped, non-segmented virus. The virion is 120–300 nm in size. The plasma membrane of the host cells serves as the source of the bilipid layer in the viral envelope. On electron microscopy, the transmembrane surface glycoprotein spikes that are 6 to 10 nm apart and 11 to 12 nm long give the virion a thistle-like look. The HRSV genome has about 15,200 nucleotides and 10 genes are encoded by it. Except for the M2 gene, which contains two overlapping open reading frames that encode two different proteins, M2-1 (the transcription processivity factor) and M2-2 (a transcriptional regulatory protein), all viral mRNAs encode a single viral protein. The RNA and related proteins such as nucleoprotein (N protein), phosphoprotein (P protein), polymerase (L protein), and M2-1 make up the nucleocapsid complex of the virion. The transmembrane surface proteins connected to the envelope are fusion protein (F protein), attachment protein (G protein), and the hypothetical viroporin (SH proteins). These proteins are essential for viral contagiousness. Viral morphogenesis benefits from the presence of the M protein (Matrix protein). According to Spann et al. (2004), the two non-structural proteins (NS1 and NS2) block type I interferon and the immunological response to viral infection in cells. This impacts the adaptive immune response to HRSV.

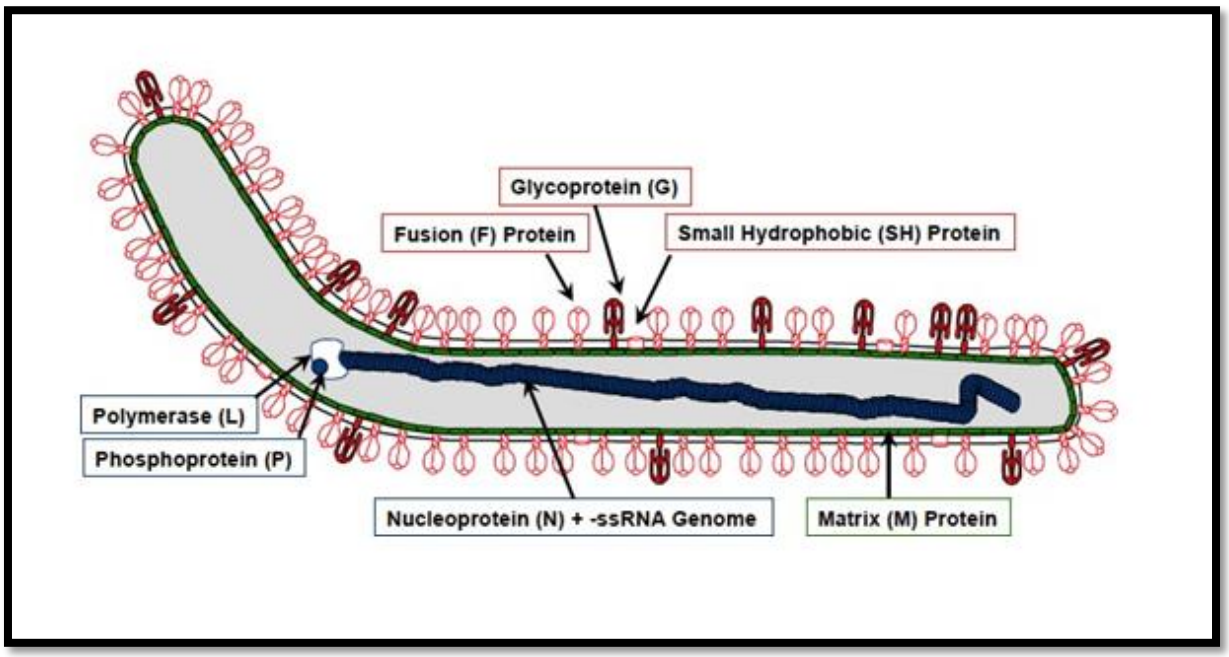

FIGURE .1. SCHEMATIC DIAGRAM OF HRSV VIRION (PANDYA *ET AL.*, 2019)

FUNCTIONS OF SURFACE PROTEINS (F PROTEIN, G PROTEIN AND SH PROTEIN)

The main immunoprotected antigens are the fusion protein (F protein) and attachment protein (G protein), which bind to CX3CR1 on epithelial cells. The key mediator of viral attachment to host cells is the G protein, a type II transmembrane protein. During infection, it is generated in membrane-bound and secreted forms. Two hypervariable sections and a core conserved domain make up the extensively glycosylated membrane-bound form. The natural version of the F protein is present, but after attachment, it changes structurally. The latter triggers viral penetration and results in the union of the host and viral membranes. The neighboring healthy cells then join forces with the infected cells to produce the distinctive RSV syncytia as a result of the F protein. According to Costello et al. (2012), the F protein is the main target for the development of antiviral drugs. A tiny hydrophobic protein with remarkable conservation, the SH protein. Although the precise function of SH protein in the HRSV life cycle is unknown, it has been demonstrated that its removal causes replication to be less robust (Bukreyev et al., 1997; Whitehead et al., 1999). By functioning as an ion channel (Gan et al., 2008), SH protein also regulates membrane permeability (Carter et al., 2010). All three surface proteins must be involved in order for the virion to fuse effectively.

HRSV ANTIGENIC VARIATION

According to the G gene's sequence analysis and antigenic variants, HRSV is traditionally split into two main antigenic groups: HRSV A and HRSV B. Multiple genotypes are created from these populations. It has been proven that both groups co-circulate when an outbreak is present. The ratio of HRSV A and B varies, nevertheless. The recently discovered HRSV B BA genotype, which has the distinctive 60-nucleotide duplication shown in figure-1, and the HRSV A ON1 genotype, which has the distinctive 72-nucleotide duplication shown in figure 2.2b, have spread quickly throughout the world (Pangesti et al., 2018). This might be as a result of population immunity pressures that favor these strains over other strains in circulation, improving viral fitness and attachment in vitro. According to recent research (Bayrakdar et al., 2018; Hibino et al., 2018; Lu et al., 2019; Jagusic et al., 2019), the ON1 and BA9 genotypes have supplanted the previously circulating genotypes and have become the prevalent HRSV genotypes in many countries. There are now 13 genotypes of HRSV A and 28 genotypes of HRSV B.

There is ongoing debate over the connection between the number of HRSV strains in circulation and the severity of an illness. While the majority of reports (Hall et al., 1990; Gilca et al., 2006; Jafri et al., 2013; Tran et al., 2013) showed HRSV A to be linked with more severe clinical disease, Hornsleth et al. (1998) identified HRSV B infection to be more severe. Other research (Fodha et al., 2007; Kaplan et al., 2008; Esposito et al.,

2015; Gamio-Arroyo et al., 2017) have not discovered a relationship between HRSV group and disease severity.

Replication of HRSV

The respiratory epithelium's ciliated cells are the target of the G protein of HRSV during viral replication. The cellular heparan sulphate, glycosaminoglycans (GAGs), and chondroitin B found in the host cells are the receptors for the G and F proteins (Hallak et al., 2000; Techaarpornkul et al., 2002). The virion penetrates the host cell and releases its genetic material for further replication after the viral envelope and host cell plasma membrane fuse via the F protein. The polyadenylation and capping of the translated mRNAs occur here (Barik, 1993; Kuo et al., 1997; Moudy et al., 2004). L, N, P, M2-1, and M2-2 are the five main proteins that contribute to the production of RNA. The primary polymerase subunit and source of the catalytic domains is the L protein. The P protein works with the N and L proteins to assemble and bind with the nucleocapsid. It is a crucial cofactor in the synthesis of RNA. The balance between RNA replication and transcription is regulated by the M2-1 and M2-2 proteins (Cowton et al., 2006). Microtubules have a role in the assembly of viral components, while actin molecules control viral release (Kallewaard et al., 2005). The replication procedure takes between 10 and 12 hours to finish.

PATHOGENESIS OF HRSV INFECTIONS

The upper respiratory tract may only be affected by the HRSV infection, or the lower respiratory tract may also get infected. In the bronchiolar epithelium, HRSV multiplies, which causes necrosis to form. Air is trapped because the tiny airways are blocked by the shed epithelium and the increased mucus secretion. Multiple areas of atelectasis eventually result from the trapped air being reabsorbed (Eiland, 2009). Viral pneumonia with the development of syncytia is caused by infection in the alveolar spaces. The most typical symptoms of LRT infection include bronchiolitis, lymphocytic peribronchiolar infiltration, and edema of the bronchial walls and surrounding tissue (Collins & Graham, 2008).

CLINICAL MANIFESTATIONS OF HRSV INFECTIONS

Mild URTIs to serious LRTIs can be caused by HRSV. The most frequent diagnoses in children younger than 1 year of age are bronchiolitis, followed by pneumonia and tracheobronchitis (Hall et al., 2009). Only 2 to 10% of HRSV cases include croup. According to Savi et al. (2011), 20% to 40% of children who have HRSV infection during their first year of life go on to develop LRTI symptoms. One of the most frequent side effects of HRSV infection in young infants is acute otitis media (Chonmaitree et al., 2008; Marom et al., 2012). According to Marom et al. (2012), the presence of HRSV in the middle ear promotes the adhesion of bacterial pathogens such S.pneumoniae, H.influenzae, and M.catarrhalis. According to Welliver et al. (2007), infants with HRSV LRTI had low oxygen saturation and spent more days in the hospital. Hospitalization and fatality rates from HRSV are higher when underlying co-morbidities including preterm and congenital heart disease are present (Welliver et al., 2010). The most frequent aftereffect of HRSV LRTI and bronchiolitis is recurrent wheeze. 30 to 50 percent of kids hospitalized with HRSV infection experienced recurrent wheezing episodes (Szabo et al., 2013a; Regnier et al., 2013).

In adults, HRSV infection severity ranges from mild to moderate. Severe HRSV infections are more common in elderly people in long-term care facilities and old age homes, as well as people with underlying chronic circulatory disease or pulmonary disease (Walsh & Falsey, 2012).

Epidemiology of HRSV

The population most at risk for hospitalization due to HRSV infection includes infants and young children. By the time they turn 2 years old, about 95% of children have HRSV infection (Hall et al., 2009). According to Stockman et al. (2012), 24% of hospitalizations caused by ALRI in North America are attributable to HRSV. In high-income nations, the in-hospital case fatality rate for HRSV-related illnesses is less than 1% (Welliver et al., 2010; Szabo et al., 2013b; Shi et al., 2017). According to Nair et al. (2010), the case fatality rate of LRTI caused by HRSV is about 2% worldwide, with low-income nations accounting for the majority of these deaths. According to numerous hospital- and community-based studies conducted in India, HRSV prevalence rates in children ranged from 5 to 54% and 8 to 15%, respectively (Broor et al., 2018). Infants had the highest incidence of HRSV, which was estimated to be 324/1000 child years (Broor et al., 2007). The existence of risk factors affects how serious an HRSV infection is. The severity of an HRSV infection in young children is more likely

to be increased by a variety of environmental, host, and socioeconomic factors. Children who are in school are also frequently reinfected with HRSV (Schanzer et al., 2006).

Seasonality of HRSV

To promptly improve preventive, diagnostic, and treatment efforts, one must be aware of the seasonality of HRSV. Globally, HRSV outbreaks often begin in the south and move north. While the HRSV peaks in the Northern Hemisphere between September and December, it does so in the Southern Hemisphere between March and June (Obando-Pacheo et al., 2018). HRSV remains for a longer period of time in nations with humid and rainy seasons that are close to the equator. The HRSV activity is at its peak in temperate areas from late fall to early spring. The HRSV activity in tropical areas is most prominent during the rainy season and may continue all year. However, the causes of the beginning and ending of HRSV activity are still unknown and are the focus of continuing study (Donaldson, 2006; Welliver et al., 2007; Noyola & Mandeville, 2008). Various epidemiological patterns of HRSV around the world may be related to the interaction of climatic conditions (Sloan et al., 2011). The stability and infectiousness of HRSV may be affected by humidity, the surrounding temperature, and sunlight. According to Panda et al. (2017), the rainy and winter seasons are when HRSV activity is most prevalent in India.

Laboratory diagnosis of HRSV infections

For HRSV infection, rapid antigen detection assays and NAATs have replaced the hitherto common diagnosis method of viral isolation. In laboratories, RT-PCR is the technique of choice for HRSV detection. The simultaneous strain identification of HRSV is possible with RT-PCR, which has consistently shown higher specificity and sensitivity than quick antigen detection techniques (Henrickson & Hall, 2007). Due to the delay in acquiring convalescent sera, serological identification of HRSV infection plays a significant role in epidemiological surveys rather than patient care. Serological diagnosis is rarely used in pediatric patients.

Prophylaxis and treatment of HRSV infections

There isn't a licensed HRSV vaccination at the moment. The preventative medication palivizumab, a monoclonal antibody against the F protein, is exceedingly expensive compared to the benefit it provides. Currently, the only treatments for HRSV infection are ribavirin aerosol or oral. After treating HRSV infections with ribavirin, there have been reported decreases in the length of mechanical ventilation, the number of days spent in the hospital, and the long-term incidence of recurrent wheeze (Turner et al., 2014). The difficulties in developing a safe and effective vaccination have hindered numerous attempts to develop an HRSV vaccine. In clinical studies, more than 16 vaccination or monoclonal antibody candidates are being examined (Broor et al., 2018).

Influenza viruses

The Orthomyxoviridae family, which has the following seven genera: Influenzavirus A, Influenzavirus B, Influenzavirus C, Influenzavirus D, Isavirus, Quaranjavirus, and Thogotavirus, is where the influenza viruses are classified. The most dangerous pathogen among the influenza kinds, influenza A virus, infects both humans and other mammals. The virus that causes pandemics is to blame. Based on the surface proteins neuraminidase (NA) and haemagglutinin (HA), influenza A viruses are further classified into a number of subtypes. There are currently 11 neuraminidase subtypes (N1-N11) and 18 haemagglutinin subtypes (H1-H18). Only a human pathogen, influenza B virus, causes less serious illnesses. The seal is another mammal that is prone to contracting influenza B. There are two distinct lineages of the influenza B virus: B/Yamagata and B/Victoria (Xu et al., 2004). Both people and pigs can contract the moderate sporadic URTI caused by influenza C virus. The influenza D and C viruses are very similar. Infections in people are not brought on by it.

CONCLUSION

In conclusion, this study investigated the evolving characteristics of HRSVs during pre-pandemic and COVID-19 pandemic periods. Our findings revealed that although there were certain differences in genetic variation and prevalence features between HRSV A and B, their evolutionary patterns remained similar before and during the pandemic. Notably, amino acid substitutions at nuetralizing antigenic sites of F protein exhibited temporal specificity. However, these substitutions did not result in any discernible alterations in viral biological properties but may have been associated with viral adaptability. It is speculated that the stringent mitigation measures implemented during the pandemic effectively controlled COVID-19 incidence and excess mortality

without placing additional immune pressure on HRSV. Nonetheless, continuous monitoring of genomic variations within HRSV remains crucial to generate scientific data for designing effective vaccines.

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