

## Review Article

# An overview of the emerging SARS-CoV-2 variants in the Middle East

Areej M. Alsyamy<sup>1\*</sup>, Taraheeb K. Alajmi<sup>2</sup>, Ibrahim F. Alamri<sup>3</sup>, Basmah F. Alamri<sup>4</sup>,  
Waseem M. Mahmoud<sup>5</sup>, Abdulrahman A. Aljohani<sup>6</sup>, Mohammed A. Almutairi<sup>7</sup>,  
Ibrahim F. Alshaikh<sup>7</sup>, Layali I. Assiri<sup>4</sup>, Asma A. Alhrthialsharif<sup>8</sup>, Hashim Y. Alnami<sup>9</sup>

<sup>1</sup>Department of Internal Medicine, King Abdullah Medical Complex, Jeddah, Saudi Arabia

<sup>2</sup>College of Medicine, Jordan University of Science and Technology, Irbid, Jordan

<sup>3</sup>College of Medicine, Medical University of Gdańsk, Gdańsk, Poland

<sup>4</sup>College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia

<sup>5</sup>Department of Home Care, Dr. Soliman Fakeeh Hospital, Jeddah, Saudi Arabia

<sup>6</sup>Department of Family Medicine, Yanbu General Hospital, Yanbu, Saudi Arabia

<sup>7</sup>College of Medicine, University of Jeddah, Jeddah, Saudi Arabia

<sup>8</sup>College of Medicine, Umm Al-Qura University, Mecca, Saudi Arabia

<sup>9</sup>College of Medicine, King Khalid University, Abha, Saudi Arabia

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### \*Correspondence:

Dr. Areej M. Alsyamy,

E-mail: areej.msss@hotmail.com

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## ABSTRACT

Studying genomic mutations and variants of severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) provides a remarkable insight into the efficacy of the novel treatment and interventional modalities, like vaccines. The Middle East is one of the most burdened countries with COVID-19. Different reports from this region reported various mutations and variants of COVID-19. Therefore, we aim to provide an overview of the emerging SARS-CoV-2 variants in the region. Evidence from studies conducted in the Middle East and North Africa (MENA) region shows a great shifting to D614G from D614 variants of SARS-CoV-2 in the region. This is also similar to the patterns reported by other investigations on a worldwide level. In addition, single experiments also reported mutations that were not previously detected elsewhere, and some studies even linked some mutations and specific COVID-19 symptoms. These findings indicate the need to conduct further research in the region to validate the importance of these mutations and relate them with the effectiveness and manufacturing of the different therapeutic and interventional approaches.

**Keywords:** SARS-CoV-2, Middle East, Variants, Genomes, Phylogeny, COVID-19

## INTRODUCTION

Early reports showed that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative agent of COVID-19. At first, reports indicated that the mutation rate of the virus was low. However, more and more recent reports indicate the relatively high rate of mutation for this virus. Furthermore, these mutations were reported to have a reduced proofreading activity and are usually related to these viruses' ribonucleic acid (RNA)-dependent RNA polymerase.<sup>1-4</sup> Therefore, the spike

glycoprotein of the virus has been an area of interest of researchers. This is because of its biological importance as it is mainly responsible for attaching the virus with its human receptors (angiotensin-converting enzyme-2).<sup>4</sup>

COVID-19 has been reported with a significant burden over the different healthcare systems and affected patients. In addition, the disease causes significant health and non-health-related complications that change various aspects of life on earth. In addition to the various morbidities and high mortality rates, evidence shows that the social and

economic burden of the disease has also been associated with significant adverse outcomes.<sup>5-7</sup> Therefore, optimizing therapeutic and interventional modalities has prioritized healthcare authorities and governments in the last months. Studying genomic mutations and variants of SARS-CoV-2 provides a remarkable insight into the efficacy of the novel treatment and interventional modalities, like vaccines.

The Middle East is one of the most burdened countries with COVID-19. Different reports from this region reported various mutations and variants of COVID-19.<sup>8,9</sup> Therefore, we aim to provide an overview of the emerging SARS-CoV-2 variants in the region.

## **METHODS**

This literature review is based on an extensive literature search in Medline, Cochrane, and EMBASE databases which was performed on 27 October 2021 using the medical subject headings (MeSH) or a combination of all possible related terms, according to the database. To avoid missing potential studies, a further manual search for papers was done through Google Scholar while the reference lists of the initially included papers. Papers discussing the emerging SARS-CoV-2 variants in the Middle East were screened for useful information. No limitations were posed on date, language, age of participants, or publication type.

## **DISCUSSION**

Evidence shows that viral mutations mainly occur to adapt to the different actions of antiviral medications. However, as these viruses are exposed to various mutation events, the resulting genomic features and related characteristics are usually harmful.<sup>10</sup> Furthermore, it has been demonstrated that the evolution rate of SARS-CoV-2 is slow. Therefore, it is noteworthy to study mutations of the virus and the associated clinical characteristics that might interest healthcare authorities regarding planning interventional and therapeutic approaches. In addition, resistance to neutralizing antibodies of the infected patients was reported with SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) infections. Accordingly, it has been shown that the risk of mortality and disease severity is high among these patients.<sup>11</sup>

Different investigations in the literature were published to report a variant analysis of COVID-19 from different countries within the Middle East. However, the findings of these investigations were not similar, and each article added to the literature about the potential presence of various COVID-19 variants and mutations within the region. Identifying these variants can significantly lead to vital information regarding tracking the sources of infections and the validity of vaccines against them. This can help healthcare authorities to enhance the response against COVID-19 and plan adequate interventions. For instance, a previous cross-sectional investigation by

Bindayna et al assessed 50 samples for possible detection of variants of SARS-CoV-2 in the Middle East.<sup>12</sup> Based on the information obtained from their analysis, the authors suggested some conclusions. It has been reported that Iran had the earliest strains with a low variant frequency based on variant alignment analysis. These results are interesting because the first announced cases of COVID-19 in the region were reported in the United Arab Emirates (UAE). Furthermore, out-group was formed in Saudi Arabia. Based on their analysis, Kuwait, Qatar, and Saudi Arabia had the highest cases per million population and the most evolved genomes.

A study from Lebanon also aimed to find the potential SARS-CoV-2 variants in 11 samples. The authors reported that they managed to detect 18 novel mutations not previously reported in the literature. These mutations include 26428A>T from E gene, 22093G>T and 22425C>T from S, 18670G>T and 19499A>C from NSP 14, 16301G>T from NSP 13, 14369G>T and 14993C>T from NSP 12 (RdRp), 12297A>T from NSP 8, 10,595T>C from NSP 5, 8897A>T from NSP 4, 6887A>T and 7766A>C from NSP 3, 6285C>A, 6281A>G/T, and 6198C>A.<sup>13</sup> Among the reported mutations, it has been reported that the most important mutations were the ones that occurred at 8651/fS and 6887A>T. These devastating mutations were reported to occur because they potentially start since the virus attacks the human body.<sup>10</sup> Moreover, it was also reported that similar mutations were also previously reported for essential genes.<sup>14,15</sup> However, the authors were not surprised by these findings. They attributed the various mutations to the different clinical characteristics of patients with COVID-19 and the widespread reported virus across the different communities globally.<sup>16</sup> In this context, a previous *in vitro* investigation from China by Yao et al demonstrated that SARS-CoV-2 mutations significantly impact blood clotting and viral infectivity functions.<sup>17</sup> Therefore, this provides solid evidence that the characteristics of COVID-19 infection are usually variable based on the infecting variant.

The majority of these described mutations were found to belong to non-structural proteins.<sup>13</sup> Reports indicate that this protein plays a major role in viral replication and interacts with other relevant proteins. Moreover, it has an essential role in suppressing the response of host interferons. In this context, a previous investigation concluded that non-structural protein-3 might lose its stability following different specific mutations.<sup>18</sup> Clinically, the Lebanese investigation also demonstrated that two patients had identical mutating changes. Although these patients had the same age, they had different prognostic outcomes. Moreover, one is a resident, and the other came from Egypt. The latter died as he had a history of a medical condition. Different mutations were reported among three patients traveling from the United Kingdom and Iran, including 11,083 T>G, 8653G>T, 1397G>A, and 884C>T.<sup>13</sup> Thus, evidence shows that RNA viruses have a high rate of mutation, which might be up to an incidence

of one mutation per day, as previously indicated with HIV.<sup>16</sup>

A previous study from Egypt aimed to evaluate the association between SARS-CoV-2 mutations and the severity of symptoms. It has been demonstrated that four highly recurrent mutations were the most prevalent in their sample, at a rate of >85%. These mutations include 14,408 (P4715L-RdRp), ORF1a at 3037 (F924\*-nsp3), 241–5'UTR, and 23,403 belonging to D614G-spike glycoprotein.<sup>9</sup> However, it should be noted that mutations were previously reported in the literature. Evidence also shows that they have similar transmission rates to the ones detected in Europe.<sup>19</sup> Besides, none of the previously mentioned variants was found in Asia, and some of them were reported in North America.<sup>16</sup> Based on various reports, evidence shows that spike glycoproteins and ORF1a polyproteins are the most common sites for variations of amino acid in the proteins of SARS-CoV-2. The different variations may not necessarily affect the clinical manifestations of the affected patients. However, there is a strong association between viral transmissibility, pathogenesis, and various mutations.<sup>20</sup> This has been indicated in the Egyptian study, which indicated that the severity of symptoms was not associated with recurrent hotspot mutations. This study also reported another variant, namely L3606-nsp6, which resulted from two deletions at the frameshift, including 11,082, and ORF1a. Clinically, it has been reported a remarkable increase in the episodes of shortness of breath, conjunctival congestion, and cough was associated with patients that had mutations in 11,082 by 200%, 1025%, and 500% times, respectively, more than other patients without these mutations.<sup>9</sup>

Another study showed that another mutation (Q677H) was found in Egypt, while another mutation (L5) was reported in Egypt, Oman, and Morocco.<sup>8</sup> The former mutation of amino acid replacements was also reported in a previous investigation. However, its clinical significance was not adequately comprehended and reported, needing further research.<sup>21</sup> The later mutation might be associated with recurrent sequencing errors and is located in the signal peptide domain of the spike glycoprotein.<sup>22,23</sup> The significance of this mutation is not also adequately elaborated.<sup>23</sup> These findings indicate the need to conduct further research in the region to validate the importance of these mutations and relate them with the effectiveness and manufacturing of the different therapeutic and interventional approaches.

Evidence from isolates in the Middle East and North Africa (MENA) region shows a rate of 15% for phylogenetic clustering, which is a meager rate.<sup>8</sup> This indicates that vast numbers of COVID-19 cases were exported into these countries. A previous investigation also conducted a clockwise analysis and showed that COVID-19 was introduced early in the region, possibly back to February 2020.<sup>8</sup> These findings can be indicated by the early reports that recorded the first COVID-19 cases in some countries, which show a similar timeline.<sup>24</sup> Mixed clusters were also

observed among the different countries in the MENA region, indicating the wide and early inter-country spread of COVID-19 among the different countries in this region. However, it has been demonstrated that no novel variants of SARS-CoV-2 were observed in samples obtained from patients in the MENA region. However, this has been reported in a single investigation in the region. It might be attributed to assessing sub-genomic parts and the whole genes in this study.<sup>25</sup>

Other studies reported distinct variants observed in the region, including S and L lineage.<sup>8</sup> However, evidence regarding the existence of these variants was controversial, and researchers called for future validating investigations.<sup>26,27</sup> Evidence from studies conducted in the MENA region shows a great shifting to D614G from D614 variants of SARS-CoV-2 in the region.<sup>8</sup> This is also similar to the patterns reported by other investigations on a worldwide level.<sup>23</sup> The estimated prevalence of D614G in the MENA region was found to be 78.7%, which is similar to the global prevalence rate of the same variant, reported to be 71%. However, it should be noted that the timeline for estimating these rates is different. Therefore, interpretation of these findings should be made with caution. The high prevalence of this variant might be attributed to the high viral load among the highly prevalent COVID-19 cases in the region.<sup>28-31</sup> However, evidence regarding an association between this variant and the severity of COVID-19 symptoms is not solid and needs further validation. Evidence regarding the prevalence of the D614G variant is supported by different investigations in the literature from the MENA region.<sup>21,32-34</sup>

A previous investigation in Saudi Arabia showed that mortality of COVID-19 patients was significantly associated with G204R/R203K mutations.<sup>35</sup> Another investigation that studied variants of SARS-CoV-2 also showed a wide range of variability, especially in Iran. It should also be noted that mutations at 14408 were not detected in the Iranian samples, while other variants were unique for this country, among others in the Middle East. Furtherly demonstrated that the highest rate of mutations was found in a Qatar sample.<sup>36</sup> Further details regarding the phylogenetic tree of variants of SARS-CoV-2 obtained from specimens in the Middle East are provided in Figure 1. These studies suggest that traveling to and from the different countries in this region is mainly responsible for transmitting SARS-CoV-2 different genomes to the area.<sup>37</sup> Another study was also conducted in Turkey to determine the potential presence of SARS-CoV-2 variants in the country. The authors reported that 293 mutations were reported among their samples, including five deletions, 12 noncoding, 124 synonymous, and 152 missense. 2421C>T (5'-untranslated region), D614G (ORF2/S), and P323L (nsp12) mutations were the most frequently observed. Moreover, it has been reported that novel mutations were also detected in aORF2/S (R995G, V1068L) and nsp12 (V111A, H133R, Y453C, M626K). These mutations are attributed to the development of nine Pangolin lineage.<sup>38</sup>

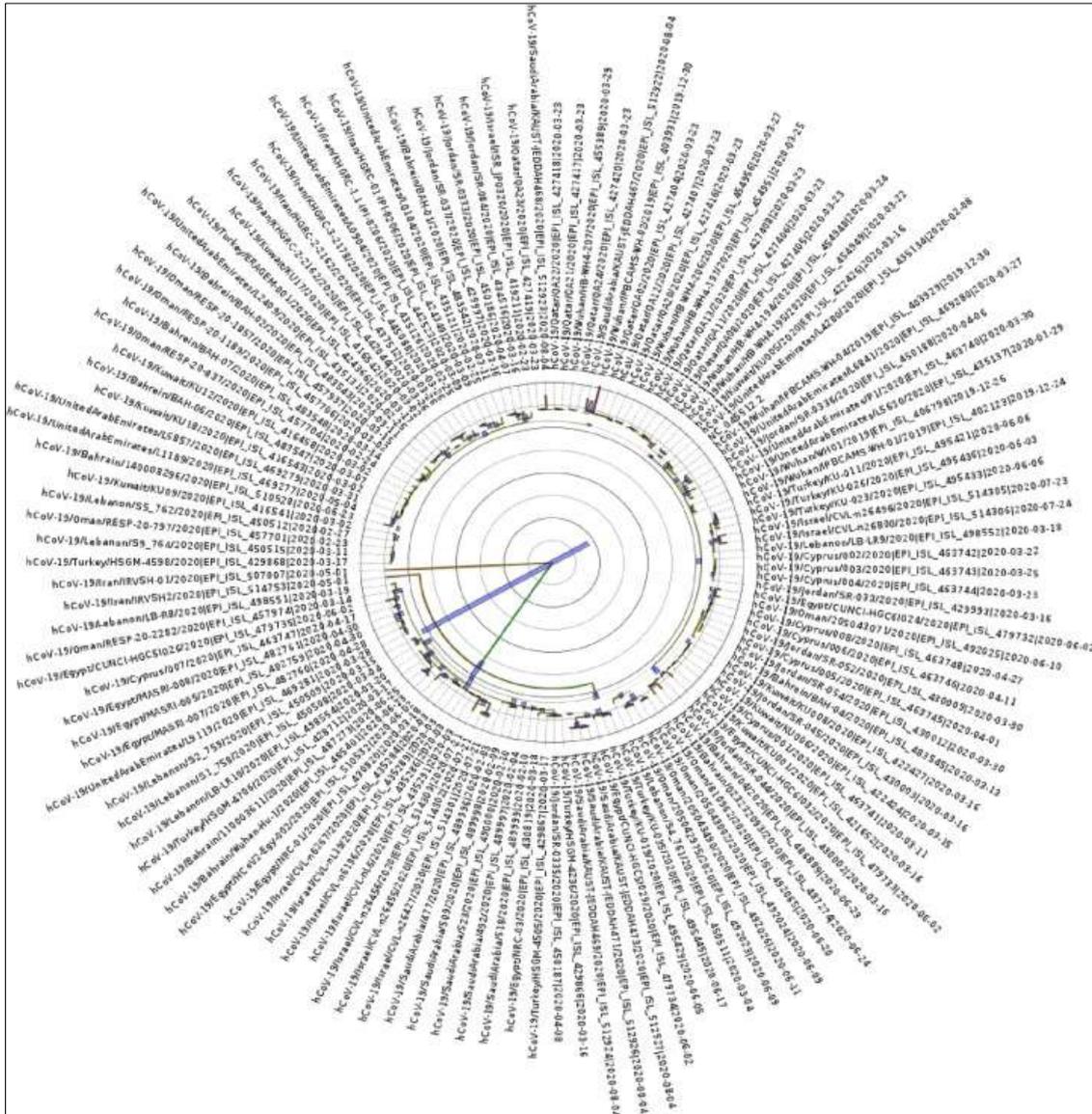


Figure 1: Phylogenetic tree for the genomes and variants of SARS-CoV-2.

**CONCLUSION**

Evidence from studies conducted in the MENA region shows a great shifting to D614G from D614 variants of SARS-CoV-2 in the region. This is also similar to the patterns reported by other investigations on a worldwide level. In addition, single experiments also reported mutations that were not previously detected elsewhere, and some studies even linked some mutations and specific COVID-19 symptoms. These findings indicate the need to conduct further research in the region to validate the importance of these mutations and relate them with the effectiveness and manufacturing of the different therapeutic and interventional approaches.

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