Detection of the new SARS-CoV-2 variant B.1.526 with the Spike E484K mutation in South America

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Article

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Abstract

Here, we report two sequences of the new SARS-CoV-2 variant recently detected and designed as B.1.526. This variant carries the immune escape-associated mutation E484K and additional mutations in the S, N, NSP2, NSP3, NSP4, NSP6, NSP8, NSP12 and NSP13 genes. Viral sequences were obtained from an individual traveling from the US to Equator with a negative RT-PCR and from one of his closest contacts that became infected. These cases should be considered an alert for the potential circulation of a new variant of concern with the E484K mutation in South America

Introduction

SARS-CoV-2 genome sequencing combined with epidemiological data is providing valuable information on new genetic variants of the virus such as the new variants of particular interest: B.1.1.7, first identified in the UK and now spreading across the world; B.1.351, first identified in South Africa and now also detected in the US, UK, Botswana, Ghana, Kenya, and Zambia; and P1, a descendant of variant B.1.1.28, identified for the first time in Brazil (1) (2) (3). These variants are of general importance as they appear to be transmitted faster and could be implicated in increased mortality and decreased vaccine efficiency (4). Of particular interest in these new variants are the presence of mutations N501Y and E484K (only present in the B.1.351 and P.1 variants) in the receptor binding domain (RBD) of the spike protein, which have been associated with increased infectivity and transmissibility (N501Y) as well as immune escape (E484K) (3)(5).

Given the availability of vaccines against SARS-CoV-2 since December 2020, the emergence of variants carrying mutations at the RBD are of particular concern. Indeed, recent studies using samples from vaccinated people have revealed a significant decrease in the potency of neutralizing antibodies against the B.1.1.7 variant, which is highly increased with the E484K-carrying variant B.1.351 (5)(6).

We identified a new variant in two samples during our epidemiological surveillance harboring the immune escape-associated mutation E484K, which GISAID classified as B.1.526. This new variant identified in an RT-PCR-negative individual traveling from the US to Ecuador at the end of December 2020 was rapidly spread amongst his close contacts indicating that it should be considered an alert for the potential circulation of a new variant of concern in South America.

Case Description And Methodology

A 33-years-old man coming from Jacksonville - United States on December 31st, 2020 to Ecuador with a negative result by Real Time PCR for SARS-CoV-2. On January 7th, the patient together with five members of his family presented mild flu-like symptoms and the diagnosis was confirmed on January 8th by Allplex™ SARS-CoV-2 assay. The symptomatology associated with the patient and his family was considered mild COVID-19, including headaches, diarrhea, and runny nose. Both nasopharyngeal swabs RNA samples from the passenger who entered Ecuador as well as that of the other member of his family,

a 59-year-old man were further analyzed with CleanPlex ® SARS-CoV-2 FLEX Panel (Paragon Genomics, Hayward, CA, USA) following the manufacturer's protocol and sequenced on MiniSeq platform (Illumina, San Diego, CA, USA) with a depth of 1000X. Assembly and annotations procedures were performed in SOPHIA-DDM-v4 and viral sequences from the patient and his relative were deposited on GISAID (https://www.gisaid.org/) with the accession numbers EPI_ISL_962493 and EPI_ISL_962492, respectively.

The phylogenetic analyses were performed with all the sequences with the mutation S:E484K available on GISAID (https://www.gisaid.org/), which were selected using the filter in mutation "Spike_E484K". Sequences were aligned with MAFFT v7.453 (7) and the maximum-likelihood phylogeny was reconstructed using FastTree Version: 2.1.12 (8).

This study was approved by the Expedited Ethics Committee of the Ecuadorian Health Ministry (MSP-DNSG-2020-10767-E)

Results And Discussion

From all the mutations identified in this new variant (Fig. 1), mutation E484K, located in the receptor-binding domain of the spike protein, has been related to ACE2 and antibody binding being considered a variant of concern. This mutation was first identified in viral sequences from Brazil and South Africa being related to reinfection cases, an increase in ACE2 binding and, most importantly, it was shown to confer resistance to neutralizing antibodies in vaccinated people (9)(10)

Bioinformatic analyses showed that the B.1.526 lineage, first detected in New York (11), presents 17 amino acid substitutions compared to the initial SARS-CoV-2 reference genome (Wuhan-Hu-1), which are the following: S: A701V, D253G, D614G, E484K, L5F and T95I; N: M234I and P199L; NSP3: P42L and Q57H; NSP8: T11I; NSP2: T85I; NSP4: L438P: NSP6: F108del, G107del and S106del; NSP12: P323L and NSP13: Q88H (Fig. 1). Mutation C14408T (P323L) on the NSP12 (RNA-dependent RNA polymerases, RdRp) protein is detected in 94% of substitutions detected in 5996 complete genomes reported in South America (Fig. S1). Although the proline to leucine substitution was proposed to not have functional consequences on RdRp (12), it is required to establish whether the loss of steric restriction imposed by the proline residue alters the functionality of RdRp (13).

The L5F mutation in the spilke protein was found in 0,6% of viral genome sequences (36 sequences) reported in South America and only 6 genomes include the pattern L5F and E484K, suggesting a low positive selection pressure. L5F is located in the signal peptide domain of the spike protein (14). Recent data using prediction algorithms indicate that this mutation could be unsuccessful because it increases the affinity of different HLA alleles and enhances CD8 T cells killing of SARS-CoV-2 infected cells (15). However, the emergence of the L5F mutation in combination with E485K should be kept under surveillance. Spike replacement of T95I does not have relevant characteristics to the virus and humans. Nevertheless, more studies are required to determine its effect.

The D253G mutation in the N-terminal domain (NTD) of Spike protein only has been found in four complete genomes sequenced in South America of the 1.432 genomes that register the mutation worldwide. Recently, D253G mutation was described as important for recognition of mAb and it may be related with scape mutation of NTD (16). E484K substitution was also reported in South Africa B.1.351 lineage (2) and Brazil P.1 lineage (17).This mutant has been reported in 13.6% of complete genomes registered in South America of the 2,683 genomes that include E484K mutation worldwide. with the biological background of this substitution, a more exhaustive genomic surveillance in South America is necessary.

D614G substitution is a dominant mutation around the world and may improve viral fitness (18) but clinical effect is yet not to be fully determined (14).

The A701V mutation has been identified in three genome sequences from South America, one from Brazil and two reported in this study (Fig. 1) according to GISAID (https://www.gisaid.org/). The A701V mutation was found in the South African lineage (B.1.351) along with the D614G mutation in mid-October. This substitution is located near to protease cleavage sites S2 subunit of Spike protein (19).

Phylogenetic analysis of 2,122 genomes presenting the E484K substitution showed that the two B.1.526 samples from South America are grouped in the cluster conformed mainly by viral sequences obtained in the US in green (Fig. 2, Table S1). The origin of this variant would not be from Brazil or South Africa, although they share point mutations with the P.1 and B.1.351 variants. It is important to determine whether the B.1.526 variant is being distributed continuously in South America. For instance, on August 11th, 2020, a sample of clade B.1.1.74 (ID: EPI_ISL_671989) was identified in the same city where B.1.526 is being reported (Fig. 2).

The introduction of a variant carrying the immune escape-associated mutation E484K mutation such as the B.1.526 in South America, and especially in Ecuador, is of utmost concern since massive access to vaccines is not equally guaranteed across countries. The rapid emergence of new variants of biological interest such as that reported in this study highlights the need to increase mobility restrictions and accelerate vaccination processes in South America, specifically in countries where vaccination is limited. Further, genomic and immune surveillance are critical to determining the impact of this new variant in SARS-CoV-2 transmission and immunity dynamics.

Declarations

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Figures

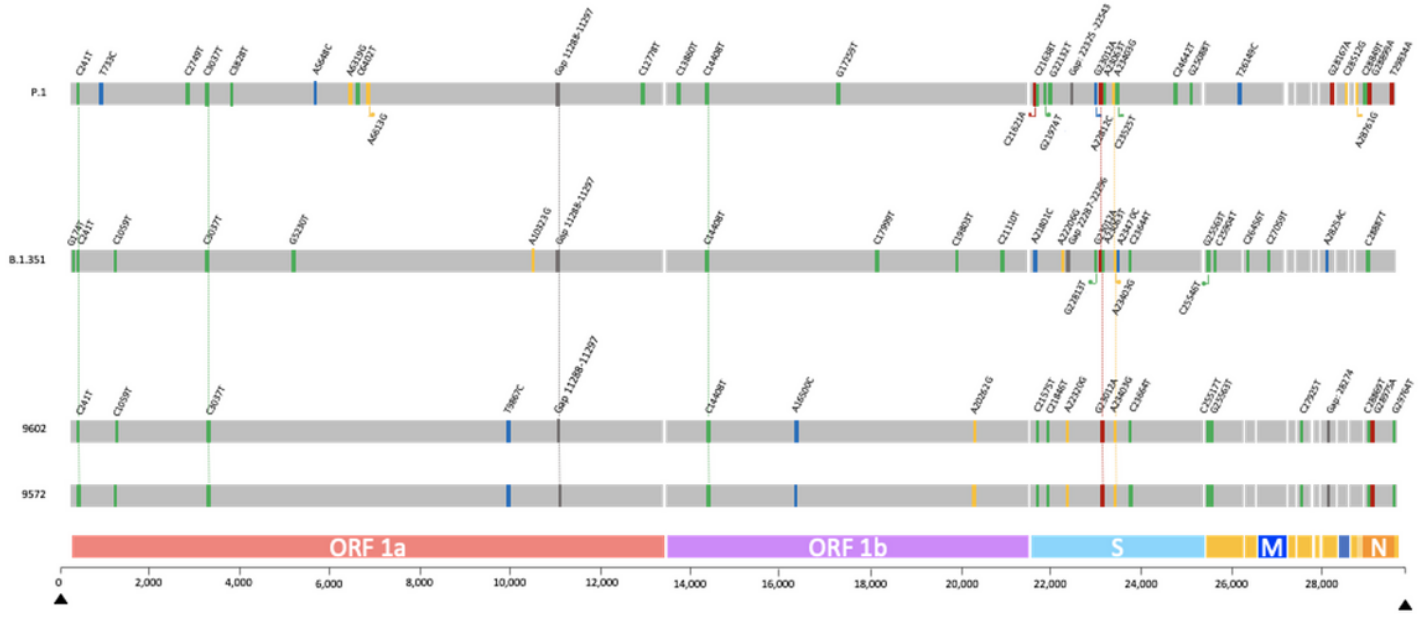

Figure 1

Map of SARS-CoV-2 variations across the viral genome found in variants isolates of Brazil (P.1), South Africa (B.1.351) and New York derived from B.1.526. Ecuadorian isolates ID: 9602 (EPI_ISL_962493), ID: 9572 (EPI_ISL_962492).

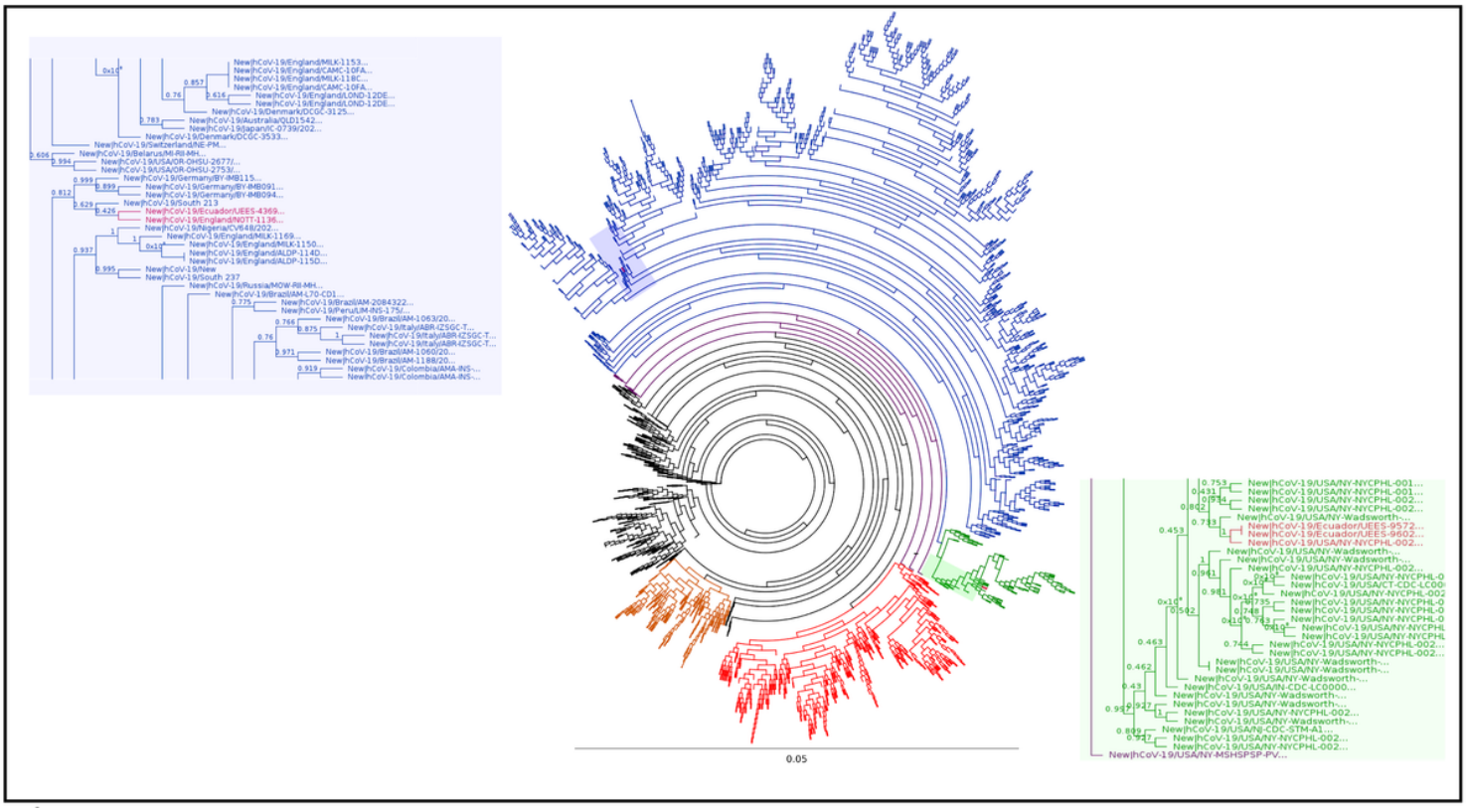

Figure 2

Phylogenetic analysis with maximum likelihood estimation of 2,122 genomes carrying the E484K substitution (February 11th, 2021). Blue branches correspond to samples mainly collected in Brazil, green areas correspond to samples mostly collected in the USA and in red and orange branches the samples were collected in South Africa.

Supplementary Files

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- Supplementarymaterial.docx