Covid 19 Variants

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ABSTRACT

The sudden wave surge in COVID-19 cases in India coincides with high prevalence of more-transmissible variants, associated with diagnostic test failures and antibody escape. These variants of concernB.1.1.7 (501Y.V1), B.1.351 (501Y.V2) and B.1.1.28.1 (501Y.V3; also known as P.1)were observed during the sudden surge in COVID-19 cases in the UK, South Africa and Brazil, respectively, with subsequent local transmission across the world. In India, the frequency of 501Y.V1 is higher than that of 501Y.V2 and 501Y.V.3.

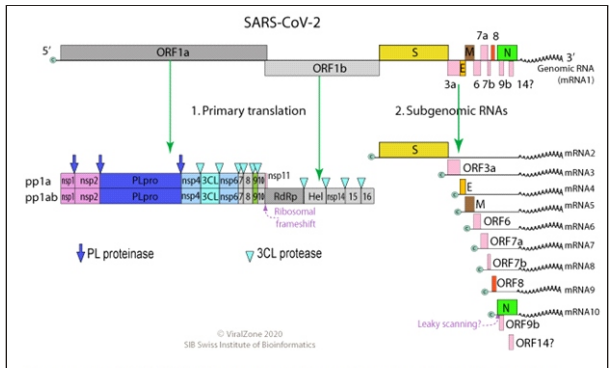
The recently found, so-called **Delta plus** variant - also known as AY.1 - spreads more easily, binds more easily to lung cells and is potentially resistant to monoclonal antibody therapy, a potent intravenous infusion of antibodies to neutralize the virus. This variant is related to the **Delta, an existing variant of concern, which was first identified in India last year** and is thought to have driven the deadly second wave of infections this summer in India.

This article will give an insight into genomics and all the variants of SARS-CoV-2 known presently with their characteristics.

1. Introduction to Genome Characteristics of Betacoronaviruses and SARS-CoV-2

Betacoronaviruses are a group of enveloped, positive-sense, single-stranded RNA viruses in the subfamily Coronavirinae in the family Coronaviridae. The genomes of these viruses, ranging from 27-32 kb in size, are the largest among RNA viruses. Each genome encodes polyproteins that undergo proteolysis to become nonstructural proteins of various functions, such as viral proteases (3CL, PL) and RNA-dependent RNA polymerase (RdRP), all of which are integral to transcription and replication. These genomes also encode several structural proteins, including spike protein (S), membrane protein (M), envelope small membrane protein (E) and nucleocapsid protein (N).

The coronavirus disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first reported in December 2019 from Wuhan, China. With its complex disease morbidity and mortality, COVID-19 has raised global concern and is characterized as a pandemic event by the World Health Organization (WHO) on March 11, 2020. Molecular features of the virus could be realized by undertesting genotypic and phenotypic properties of the viruses. Whole genome sequence (WGS) data is an excellent resource in understanding the evolution of the virus, assist in tracing pathways promoting infection, etc; understanding of which can assist in the development of diagnostics, therapeutic and preventive strategies.



The genome of SARS-CoV-2 showing transcription sites and protein coding domains.

Source: https://viralzone.expasy.org/resources/nCoV_genome_bis.png

The first genome sequences of the novel betacoronavirus became available on the global public repository, Global Initiative on Sharing All Influenza Data (GISAID) (https://www.

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gisaid.org/) around 10 January 2020, named as the original virus from Wuhan (WIV 04-reference or hCoV-19/Wuhan/WIV04/2019). India was the 5th country in the world to sequence the viral genome (isolated from the first patients in Kerala) for inclusion in GISAID.

2. Importance of Mutations

Over time, viruses accumulate mutations that alter the genomic sequence, either due to random replication errors or via a defense mechanism of the host called RNA editing. The mutations are called synonymous when there is no change to the amino acid encoded and non-synonymous when the protein acquires a change due to the mutation. SARS-CoV-2 has acquired new mutations at the rate of *2 changes per month so far. (How a virus changes to a new variant? https://www.youtube.com/watch?v=qD8dAbov5JU&t=31s)

Phylogenetic analysis of the GISAID sequences highlights multiple clusters of related genomes, called clades, grouped based on common mutations. Clade O was the ancestral type which originated from Wuhan.

The D614G mutation replaced the 614th amino acid D (aspartic acid) with G (glycine) in the Receptor Binding Domain (RBD) of the Spike protein. Glycine being a less bulky amino acid than aspartic acid it is believed to contribute to a more flexible hinge region in the Spike that enables more efficient cutting for receptor binding. This offered the virus a selective advantage in infection and transmission, making it predominant all over the world. At present, almost all new infections of COVID-19, in India as well as globally, are by viruses containing this mutation.

The mutation landscape of SARS-CoV-2 has been under constant global scrutiny to understand the effect of these changes on the infectivity and antigenicity of the virus. While most mutations are of little to no consequence, sometimes the virus acquires a mutation that gives it an advantage over other strains. The Spike protein is used by the virus to enter human cells via the ACE2 receptor. Thus, Spike mutations can potentially facilitate better affinity or binding and enable easier entry into the host cell, as seen in the case of the D614G. The receptor-binding domain (RBD) in the spike protein is the most variable part of the coronavirus genome. Mutations can putatively also render the virus resistant to neutralization by host antibodies and thus need to be identified and monitored for the efficacy of antibody therapeutics.

3. Rise of virus variants

November and December 2020 brought much activity regarding both positive and negative developments. In early November 2020, an outbreak of SARS-CoV-2 in Danish mink farms with spill-over back into humans was reported 137. The virus seemed to have potentially adapted to mink by introducing a Y453F mutation into the spike protein RBD (in addition to other mutations). This led to the mass culling of mink in Denmark and, as a result, more attention started to be given to variant viruses, including Cluster 5 variants in Europe that carry the N439K mutation in the RBD. Both Y453F and N439K have been shown to affect neutralization by some SARS-CoV-2-specific monoclonal antibodies, although other antibodies are unaffected, which makes it unlikely that these two mutations alone would impair vaccine effectiveness.

Additional variants of concern were described in December 2020, such as the UK-origin variant (B.1.1.7), which seems to be more infectious than other variants and is spreading quickly in the UK and elsewhere. This variant carries several mutations, including N501Y in the RBD and a truncation of open reading frame 8 (ORF8). Although the increase in transmissibility is highly concerning, evidence so far indicates that the current vaccines retain significant levels of protection against B.1.1.7.

Other variants of concern, especially the South African origin variant B.1.351, which also carries a mutation at position 501 in the RBD (and other mutations at positions 417 and 484), is now shown to reduce the neutralization capacity and efficacy of certain vaccines.

4. Virus variants at present circulating across the globe

To inform local outbreak investigations and understand national trends, scientists compare genetic differences between viruses to identify variants and how they are related to each other.

SARS-CoV-2 Interagency Group (SIG) established by the US Department of Health and Human Services (HHS) focuses on the rapid characterisation of emerging variants and actively monitors their potential impact on critical SARS-CoV-2 countermeasures, including vaccines, therapeutics, and diagnostics.

US government interagency group developed a Variant Classification scheme that defines three classes of SARS-CoV-2 variants:

4.1. Variant of Interest

4.2. Variant of Concern

4.3. Variant of High Consequence

1. Variant of Interest

A variant with specific genetic markers that have been associated with changes to receptor binding, reduced neutralization by antibodies generated against previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity.

2. Variant of Concern

A variant for which there is evidence of an increase in transmissibility, more severe disease (e.g., increased hospitalizations or deaths), significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures.

Possible attributes of a variant of concern :

In addition to the possible attributes of a variant of interest

- Evidence of impact on diagnostics, treatments, or vaccines
  - Widespread interference with diagnostic test targets
  - Evidence of substantially decreased susceptibility to one or more class of therapies

Name	Spike Protein Substitutions	First Detected
P.2	**Spike :** E484K, (F565L*), D614G, V1176F	Brazil - April 2020
B.1.617.3	**Spike :** T19R, G142D, L452R, E484Q, D614G, P681R, D950N	India - October 2020
B.1.526.1	**Spike :** D80G, 144del, F157S, L452R, D614G, (T791I*), (T859N*), D950H	United States (New York) - October 2020
B.1.526	**Spike :** (L5F*), T95I, D253G, (S477N*), (E484K*), D614G, (A701V*)	United States (New York) - November 2020
B.1.617.1	**Spike :** (T95I), G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	India - December 2020
B.1.617.2	**Spike :** T19R, (G142D), 156del, 157del, R158G, L452R, T478K, D614G, P681R, D950N	India - December 2020
B.1.617	**Spike :** L452R, E484Q, D614G	India - February 2021

WHO label	Pango lineage	GISAID clade/lineage	Nextstrain clade	Earliest documented samples	Date of designation
Epsilon	B.1.427/B.1.429	GH/452R.V1	21C	United States of America, Mar-2020	5-Mar-2021
Zeta	P.2	GR/484K.V2	20B/S.484K	Brazil, Apr-2020	17-Mar-2021
Eta	B.1.525	G/484K.V3	21D	Multiple countries, Dec-2020	17-Mar-2021
Theta	P.3	GR/1092K.V1	21E	Philippines, Jan-2021	24-Mar-2021
Iota	B.1.526	GH/253G.V1	21F	United States of America, Nov-2020	24-Mar-2021
Kappa	B.1.617.1	G/452R.V3	21B	India, Oct-2020	4-Apr-2021
Lambda	C.37	GR/452Q.V1	20D	Peru, Aug-2020	14-Jun-2021

- Evidence of significant decreased neutralization by antibodies generated during previous infection or vaccination
- Evidence of reduced vaccine-induced protection from severe disease

- Evidence of increased transmissibility
- Evidence of increased disease severity

3. Variant of High Consequence

A variant of high consequence has clear evidence that prevention measures or medical counter measures (MCMs) have significantly reduced effectiveness relative to previously circulating variants.

Possible attributes of a variant of high consequence :

In addition to the possible attributes of a variant of concern

- Impact on Medical Countermeasures (MCM)
  - Demonstrated failure of diagnostics
  - Evidence to suggest a significantly reduction in vaccine effectiveness, a disproportionately high number of vaccine breakthrough cases, or very low vaccine-induced protection against severe disease
  - Significantly reduced susceptibility to multiple Emergency Use Authorization (EUA) or approved therapeutics
  - More severe clinical disease and increased hospitalizations

A variant of high consequence would require notification to WHO under the International Health Regulations, reporting to CDC, an announcement of strategies to prevent or contain transmission, and recommendations to update treatments and vaccines.

Selected Characteristics of SARS-CoV-2 Variants of Concern

Name Pango Lineage external Icon	Spike Protein Substitutions	WHO Label	First Detected
B.1.1.7	69del, 70del, 144del, (E484K*), (S494P*), N501Y, A570D, D614G, P681H, T716I, S982A, D1118H (K1191N*)	Alpha	United Kingdom
B.1.351	D80A, D215G, 241del, 242del, 243del, K417N, E484K, N501Y, D614G, A701V	Beta	South Africa
B.1.427	L452R, D614G	Epsilon	United States-(California)
B.1.429	S13I, W152C, L452R, D614G	Epsilon	United States-(California)
P.1	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	Gamma	Japan / Brazil

WHO label	Pango lineage	GISAID clade/lineage	Nextstrain clade	Earliest documented samples	Date of designation
Alpha	B.1.1.7	GRY (formerly GR/501Y.V1)	20I (V1)	United Kingdom, Sep-2020	18-Dec-2020
Beta	B.1.351	GH/501Y.V2	20H (V2)	South Africa, May-2020	18-Dec-2020
Gamma	P.1	GR/501Y.V3	20J (V3)	Brazil, Nov-2020	11-Jan-2021
Delta	B.1.617.2	G/478K.V1	21A	India, Oct-2020	VOI: 4-Apr-2021 VOC: 11-May-2021

*** Currently there are no SARS-CoV-2 variants that rise to the level of high consequence.**

5. Recent variant in India

DELTA PLUS Variant

India has classified a new variant of the coronavirus first identified in Europe as a "variant of concern". The Delta Plus variant, which is a mutation of the widespread Delta strain first identified in India, could be more infectious and cause more severe COVID-19. Officials in India labeled it a "variant of concern". Delta plus has the K417N mutation, which along with other another mutation, K417T, is a change in the spike protein.

According to INSACOG, a consortium of 28 labs set up by the Health Ministry to carry out genome sequencing of the virus, among the 45,000 samples from across 12 states that have been sequenced, some 48 have been found with the Delta plus mutated variant.

A mutation is elevated from a "variant of interest" to a "variant of concern" when it shows evidence of fulfilling at least one of the several criteria, including easy transmission, more severe illness, reduced neutralization by antibodies or reduced effectiveness of treatment and vaccines.

Studies are under way, but at present it cannot be said there is an increase in transmission of the Delta Plus variant based on genomic data or lab

studies; But studies have also showed that Delta Plus variant- also known as AY.1 - spreads more easily, binds more easily to lung cells and is potentially resistant to monoclonal antibody therapy.

6. Recent variant - LAMBDA VARIANT

After B.1.1.7 (Alpha); B.1.351 (Beta); P.1 (Gamma); B.1.427 and B.1.429 (Epsilon); B.1.617.2 (Delta); and Delta Plus variant, another new variant has been discovered in the world, called Lambda variant.

The Lambda variant was first originally discovered in Peru and the World Health Organization (WHO) has classified it as a "Variant of Interest" on June 14.

According to WHO, Lambda variant has multiple mutations in the spike protein that could have an impact on its transmissibility.

- The Lambda variant or C.37 variant has already been reported as highly prevalent in Peru.
- The Lambda variant lies within the B.1.1.1 lineage.
- As per the WHO, the Lambda variant is related to 81% of the cases detected since April in Peru.
- The Lambda variant has been identified in as many as 29 countries, including North and South America, Europe, and Oceania.

7. Why Strain Surveillance is Important for Public Health

Viruses generally acquire mutations over time, giving rise to new variants. Some of the potential consequences of emerging variants are the following :

- Ability to spread more quickly in people.
- Ability to cause either milder or more severe disease in people.
- Ability to evade detection by specific viral diagnostic tests.
- Decreased susceptibility to therapeutic agents such as monoclonal antibodies.
- Ability to evade natural or vaccine-induced immunity.

8. Summary

So far, India has detected Delta and Delta Plus variants in India. However, experts believe that the opening of international air travel might bring a cocktail of new variants, including Lambda in India.

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