

D614G mutation now the dominant variant in the global COVID-19 pandemic

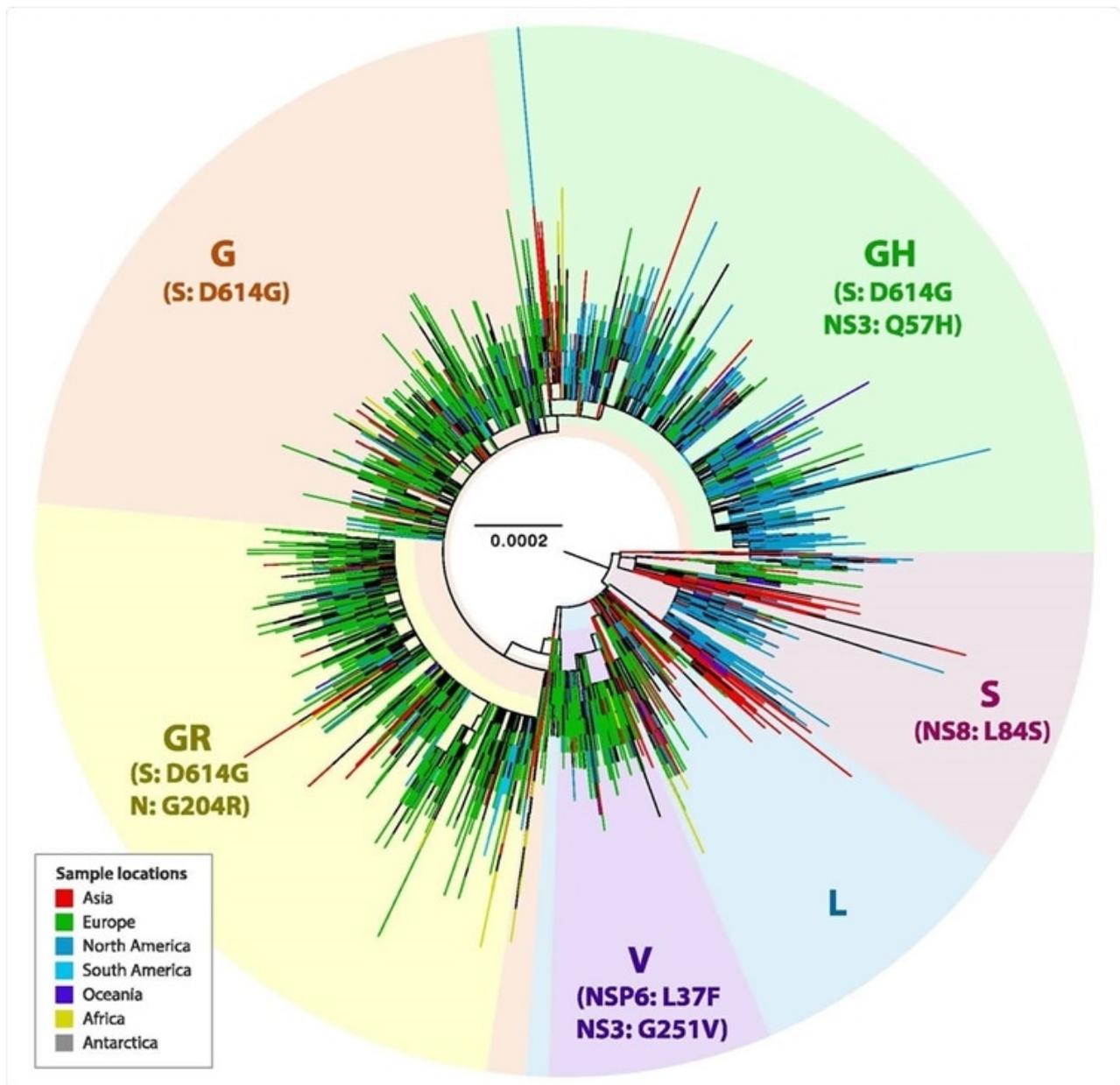


By Dr. Liji Thomas, MD

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Multiple studies show the occurrence of various mutations defining different clades of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is essential to keep watch over the newly emerging mutations and the fitness of the new strains to maintain an effective response to the pandemic. Now, a new study by researchers at the University of Hong Kong and published on the preprint server *medRxiv** in September 2020 shows that a significant variant characterized by the D614G mutation has higher infectivity, which may account for its rapid rise to the dominant position in all regions where it has emerged.

The D614G mutation is one where the aspartic acid residue at position 614 is replaced by glycine. This is at the carboxy-terminal end of the S1 domain of the SARS-CoV-2 spike protein. This mutant occupies an increasing proportion of detected variants since the end of February 2020, which has made it the most commonly identified variant in many parts of the world at present. This has led many researchers to hypothesize that it is capable of faster or easier spread compared to the wildtype virus D614, perhaps due to more rapid growth or faster viral replication, or a more significant reproduction number.



Global phylogeny of SARS-CoV-2. The maximum likelihood tree was inferred from the alignment of 26,244 worldwide SARS-CoV-2 genome sequences with high sequencing coverage, using GTR+CAT substitution model in FastTree program. Multiple clades are highlighted, and their associated mutations are indicated within parenthesis. Tree tips corresponding to the viral sequences from different continents are annotated in different colors as shown in the color legend box.

Many studies in vitro confirm the increased infectivity of this model. Phylogenetic analyses also show a phenomenon called diversifying selection at position 614, again suggesting that D614G is more infectious. The current study aims to assess its epidemiological fitness of this variant in quantitative terms, using data acquired from COVID-19 surveillance and RNA sequencing data to get an idea of how infectious it is in relation to other strains.

D614 and G614 in Co-Circulation

Global phylogenetic relationship tracing shows that the G614 mutation is found in the clade with the largest number of strains. The researchers made a crucial assumption that this is the only mutation in this clade that is associated with higher viral transmission rates.

On this basis, they analyzed over 35,000 viral sequences from the period between 24 December 2019 and 8 June 2020, all of which included the position of interest in the spike encoding gene. They identified the phylogenetic clusters of local transmission on a country-wise basis using the global viral sequencing patterns.

They defined clusters which began with one or a small number of viral introductions, with at least two sequences fitting the study criteria. In some countries, both the variants were circulating together in local clusters for two weeks or more. This would include at least two generations of the virus if the generation time is taken to be 5-7 days on average.

All the ten countries included in this analysis had a hundred circulating sequences at least during this period when two or more strains were in circulating at the same time in one cluster. This analysis, therefore, included ~500 D614 clusters and ~1,400 G614 clusters among ~11,000 sequences.

The investigators found that over time the ratio of the G614 strain to the D614 strain increased to become the dominant strain in every country.

G614 Transmission Fitness

The researchers also compared the basic reproduction number and the mean generation time of both strains. Given the assumption that the D614 strain has a mean generation time of ~5 days, the researchers calculated that the G614 strain has a reproduction number 31% times higher than the D614 strain.

The estimate above is based on the number of confirmed cases, but if deaths are used instead, the result would be a 23% higher reproduction number.

The basic mean generation time is similar for both strains, however, in terms of both confirmed cases and confirmed deaths. This fits the hypothesis perfectly and agrees with the observations gathered concerning the proportion of G614 isolates over all the countries in the study.

The researchers also looked at differences in reproduction number by geographical locations. They found that the estimates were 1.13 for the US, 1.53 for the UK, and 1.30 for other locations.

They then adjusted their analysis to ignore imported sequences that did not cause significant secondary infections. The global phylogenetic tree shows that it is possible that large numbers of imported G614 cases during the study period arrived from countries where the outbreak had gone mostly undetected, but this was the dominant strain.

Thus, the researchers next integrated the imported G614 cases into their fitness analysis on the assumption that all importations consisted solely of G614. They then estimated the imported force of G614 infection in terms of its ratio to the local incidence of COVID-19 – which was below 0.0012 in the UK.

The significance of this is its suggestion that the increase in the proportion of G614 was not due to imported cases in the UK. If so, the overall estimate of 0.0172 for all ten countries indicates that the increase in number and size of G614 clusters was due to the more efficient replication and spread of this strain relative to D614. This was so even after adjusting for cluster size or the exact definition used to trace phylogeny.

How G614 Fitness Affects SARS-CoV-2 Transmission

The estimations above indicate that the threshold for herd immunity would be higher for G614 relative to D614, since, at the basic reproduction number ratio of 1.31 it would move up from 50% to 62% for an R_0 of 2, and from 67% to 75% for R_0 of 3. If mobility, susceptibility, and infectivity are accounted for, this will result in a more accurate estimate of the herd immunity threshold.

In short, the increased infectivity of the G614 strain is solely responsible for

its higher transmission rate.

Earlier studies show that the G614 strain entered European countries earlier relative to Australia or the US, and made up from ~20% to 75% of all infections by early March. Again, New York had an earlier importation of this strain compared to Washington State. Assuming the same generation time, this indicates that the basic reproduction number was 25% higher for Washington State. However, the lack of co-circulation did not allow G614 fitness estimation for New York State.

The study thus suggests that the G614 strain has a transmission rate about a third higher than the D614 strain, which has driven its dominance in every country it has reached so far. In fact, it became the predominant SARS-CoV-2 strain in Europe within two months of its introduction.

The growth rate of G614 is 21% faster than that of D614, and this also matches the rate of resurgence of the G614-dominant virus in Beijing relative to the spread of the original D614-dominated virus in the first wave, at 325 vs. 156 local cases for the second wave compared to the first wave, within the same number of days, and despite the tight containment measures prevailing in the city.

However, there is a possibility that a more significant number of mild cases were picked up the second time around because of the higher rate of community testing from June onward. There is no evidence of higher virulence, however, and in fact, crude analyses show a higher percentage of asymptomatic, mild, or moderate cases in the second wave.

Implications

The higher infectivity and reproduction number means that preventive measures against the D614 strain will be only 70% as efficient against the G614 strain. This means that both the vaccine coverage and the herd immunity threshold will rise significantly with the G614 strain.

Of course, it could be that the R0 remained the same, but the G614 strain has a shorter doubling time by about 20%, requiring 20% faster contact tracing and control to prevent future outbreaks. This will not change the vaccine coverage required to stop the pandemic, however, due to the unchanged R0.

More research will be required to understand how other mutations in strains with the D614G mutation affect transmissibility and generation time. The fitness estimates apply only with co-circulation of both these strains and not if only one new strain is emerging or is already the dominant strain, nor if three or more strains are circulating simultaneously.

The scientists conclude, *"The G614 mutation confers a transmission advantage over the wildtype D614. Our method can be readily integrated into the current COVID-19 surveillance system, to provide efficient epidemiological assessment of the transmission potential of emerging mutants for early alert."*

*Important Notice

medRxiv publishes preliminary scientific reports that are not peer-reviewed and, therefore, should not be regarded as conclusive, guide clinical practice/health-related behavior, or treated as established information.

Source

Journal reference:

- Leung, K. et al. (2020). Empirical Transmission Advantage Of The D614G Mutant Strain Of SARS-Cov-2. *medRxiv* preprint doi: <https://doi.org/10.1101/2020.09.22.20199810>, <https://www.medrxiv.org/content/10.1101/2020.09.22.20199810v1>
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Written by

Dr. Liji Thomas

Dr. Liji Thomas is an OB-GYN, who graduated from the Government Medical College, University of Calicut, Kerala, in 2001. Liji practiced as a full-time consultant in obstetrics/gynecology in a private hospital for a few years following her graduation. She has counseled hundreds of patients facing issues from

pregnancy-related problems and infertility, and has been in charge of over 2,000 deliveries, striving always to achieve a normal delivery rather than operative.