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Commentary

Virus genomics as a clinical and epidemiological tool

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In this article of EBioMedicine [1], Lorenzo-Redondo et al. use whole genome sequencing to compare the epidemiology of three SARS-CoV-2 clades that spread in Illinois during the early phase of the COVID-19 pandemic. One of these clades was defined by the now-infamous D614G substitution. Viral lineages in which the 614th amino acid of the Spike protein changed from aspartate (D) to glycine (G) now constitute the majority of SARS-CoV-2 in global circulation [2]. This study finds the correlate: a clade containing the D614 variant detected in Chicago was geographically limited in spread and was associated with lower viral loads among infected individuals. Taking this perspective, the authors consider the multi-dimensional selective forces that influence SARS-CoV-2 evolution and impact the way in which this virus interacts with our immune system.

When a new viral lineage dominates the virus population to the extent that the G614 variant has, there are two likely explanations. Either the emergent variant has a fitness advantage over its predecessors or some stochastic event occurred to enable that lineage to replicate with relatively little competition. Determining which scenario applies to D614G requires that we consider the comparative fitness of the two genotypes. Biochemically, the exchange of a negatively charged amino acid (D) for a non-polar one (G) slightly modifies the configuration of the Spike protein trimer so that the receptor binding site, which interacts with the human ACE2 receptor, is more readily exposed [3,4]. Consistent with this hypothesis, a preliminary in vitro study found that pseudoviruses containing the G614 variant were more infectious in cell culture compared to their D614 counterparts [5]. Gaining entrance into host cells is the key first step in the virus replication cycle. Therefore, a virus that can latch onto a host cell receptor more easily has a competitive edge. To be sure, it is a far leap between tissue culture and a human being, but Lorenzo-Redondo et al. and others observe that infection with the G614 variant is associated with significantly higher viral loads in the upper respiratory tract of COVID-19 patients [1,5]. These data provide a blueprint for the bridge between the molecular and physiological, and, taken together, indicate that the D614G substitution did confer a fitness advantage.

It is more complex to disentangle the impact of these variants on clinical outcome because the virus' opponents within the host are not as obvious. There is a concern that SARS-CoV-2 could evolve to resist neutralization by antibodies elicited naturally during infection or by a vaccine adjuvant [6]. As new vaccines and therapeutics are distributed, the virus may find ways to evade them, but it does not seem to have done so yet [3]. Though Lorenzo-Redondo et al. do not directly address this possibility, they contribute to the body of evidence demonstrating that viral load is not correlated with disease severity [1,5,7]. Thus, it may be that evasion of this immunological line of defense plays a crucial role in promoting transmission of SARS-CoV-2 without substantially impacting clinical outcome.

There are a number of other host characteristics that could influence the variant/outcome relationship that must be identified and controlled for before a consensus on this subject may be reached [8,9]. Lorenzo-Redondo et al. adopt this approach by fitting a logistic regression model to evaluate the impact of clade, viral load, and demographic variables on disease severity among the patients in their cohort. They were unsuccessful in finding a statistically significant link between virus clade and disease severity [1], and their findings are largely consistent with the literature [5,7]. As a notable exception, an analysis of case fatality rates and the prevalence of the G614 variant in different countries did find a significant positive correlation between the two [10]. But to conclude from this study that the G614 variant increases the risk of death among infected individuals would be to commit an ecological fallacy. Of course, a lack of evidence does not necessitate that no connection between variant and outcome exists, and the accumulation of data along with the application of more sophisticated statistical methods may ultimately reveal that this substitution does bear clinical relevance. However, at this time, the data suggest that the D614G substitution affects virus-virus competition without influencing key host-virus interactions that determine a patient's prognosis.

In sum, Lorenzo-Redondo et al. present an apt case study on the role of virus genomics in epidemiology and clinical practice. The D614G substitution is one example of how SARS-CoV-2 is evolving. Continuing to use whole genome sequencing as an epidemiological tool will facilitate the rapid detection and monitoring of new SARS-CoV-2 variants when they emerge. In the interim, diversity in the host immunological response should be of primary concern in the clinic and in vaccine design. We are unlikely to find a universally effective medical solution, at least in the short term. Therefore, it is imperative that we develop a diverse arsenal of therapeutic strategies

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to treat individuals suffering from COVID-19 and to prevent new infections going forward.

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Declaration of Completing Interest

The author declares no conflicts of interest

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