The SARS-CoV-2 Spike Variant D614G Favors an Open Conformational State

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The COVID-19 global pandemic is an international health emergency. It is caused by the SARS-CoV-2 virus, which binds with its trimeric Spike protein to the ACE2 receptor in the human lung. Early in 2020, researchers observed the emergence of a single amino acid variant at residue 614 of the Spike trimer, in which the aspartic acid of the original "D-form" was replaced by a glycine in the emergent "G-form." The G-form rapidly became the most dominant form, displaying heightened infectivity and transmissibility. To gain understanding of the molecular mechanisms underlying how a single amino acid shift could cause such a drastic change, we performed extensive all-atom simulations of the Spike trimer in explicit solvent in both the D-form and the G-form. For each form, we simulated the "all down" conformational state, which is not infection-capable, and the "one up" state, which is infection capable due to the "blossomin" outward of one of the three trimers. We show that a shift in the inter-protomer contacts likely leads to a shift in energetics that causes the G-form to have a heightened population of Spikes in the one up state. While there is no significant difference between the exposure of the ACE2 binding site when comparing the D- and G-forms, there is a difference when comparing the all down and one up states, so a heightened population in the one up state corresponds to higher infectivity. We also investigate antibody binding and demonstrate that steric hindrance may be responsible for differential neutralization by monoclonal antibodies. Overall, this work presents molecular-level understanding of the differences between the D- and G-forms that is of crucial importance for vaccine design.