

Intrasubtype reassortments cause adaptive amino acid replacements in H3N2 influenza genes

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Influenza A is a rapidly evolving RNA virus with genome composed of eight distinct viral segments. This genetic structure allows formation of new combinations of segments when a cell is coinfecting by multiple viral strains, in a process called reassortment. Reassortments between strains and point mutations are two major contributors to diversity of Influenza A virus; however, the link between these two processes is unclear. It has been suggested that reassortments provoke a temporary increase in the rate of amino acid changes as the viral proteins adapt to new genetic environment, but this phenomenon has not been studied systematically.

Here, we use a phylogenetic approach to infer the reassortment events between the 8 segments of influenza A H3N2 virus since its emergence in humans in 1968. We then study the amino acid replacements that occurred in genes encoded in each segment subsequent to reassortments. In five out of eight genes (NA, M1, HA, PB1 and NS1), the reassortment

events led to a transient increase in the rate of amino acid replacements on the descendant phylogenetic branches. In NA and HA, the replacements following reassortments were enriched with parallel and/or reversing replacements; in contrast, the replacements at sites responsible for differences between antigenic clusters (in HA) and at sites under positive selection (in NA) were underrepresented among them.

Post-reassortment adaptive walks contribute to adaptive evolution in Influenza A: in NA, an average reassortment event causes at least 2.1 amino acid replacements in a reassorted gene, with, on average, 0.43 amino acid replacements per evolving post-reassortment lineage; and at least ~9% of all amino acid replacements are provoked by reassortments.