LETTER

A consideration of within-host human cytomegalovirus genetic variation

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In Cudini et al. (1), the authors suggest that earlier work has argued high levels of intrahost variation in human cytomegalovirus (HCMV) to be the result of exceptionally fast mutation rates (on par with RNA viruses), citing our recent review (2) as evidence. In reality, ref. 2 noted that levels of variation can be comparable to those observed in certain RNA viruses (as Cudini et al. reconfirm), and that this required explanation "in light of the low mutation rates of herpesviruses relative to those of RNA viruses." In the summarized primary literature, ref. 3 argued that fast mutation rates could explain this observation, but that "this possibility does not seem likely considering that HCMV encodes a DNA polymerase with proofreading activity." Directly estimating de novo mutation rates from longitudinal samples, ref. 4 found them to be consistent with murine cytomegaloviruses, and multiple orders of magnitude slower than many RNA viruses.

Based upon this incorrect premise, Cudini et al. (1) go on to suggest that high levels of variation are, instead, a consequence of so-called "mixed" infections, concluding with a presentation of patient samples argued to be consistent with "mixed" or "single" infection histories. Yet, in making this claim, they recapitulate earlier (uncited) work. Ref. 5 previously examined the role of multiple-population infection and argued it to be a highly important and underappreciated player, similarly describing patient samples consistent with single- and multiple-population transmissions, but taking the additional step of inferring patient-specific demographic/infection histories.

Cudini et al. (1) also overlook other studies describing additional key processes. The severity of the infection bottleneck, and the population structuring and gene flow associated with compartmentalization, have all been shown to be significant determinants (6, 7). Additionally, by inferring genome-wide recombination rates in HCMV, ref. 8 found recombination to be positively correlated with variation—suggesting the pervasive effects of background selection (9). By modeling these selective and demographic processes jointly, ref. 10 demonstrated an ability to fit both observed within- and between-patient data. Cudini et al. do not account for these processes—neither the timing of the infection-related bottleneck relative to their patient sampling nor the purifying selection effects inherent to the 10-kb RL11D region that they consider.

Notably, the choice of this small region stems from an attempt to shoehorn phylogenetic approaches into the analysis of recombining, within-population data. As demonstrated in all of the above citations, however, the utilization of a population genetic framework allows for a direct consideration of recombination events—thereby allowing for the appropriate genome-wide analysis of locus-specific coalescent trees, as opposed to their struggle to identify a genomic region small enough to allow for the pretension of a single phylogeny.

In sum, the mutation rate-based claim upon which Cudini et al. (1) rely for motivation is inaccurate, the primary results pertaining to multiple-population infection were previously described, the analysis framework is incomplete, and the neglect of other key variation-determining evolutionary processes renders the interpretations questionable.

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