Evolutionary Dynamics of Norovirus Infection in Immunocompromised Hosts

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Background/Objective
Norovirus (NoV) is a clinically important RNA virus that causes acute gastroenteritis and is associated with global epidemics of disease. While the majority of NoV infections are mild and self-limiting (symptomatic 1-3 days), infection within an immunocompromised host can result in severe and prolonged illness (lasting months to years) with limited treatments available. A common feature of these prolonged NoV infections are high rates of evolution with exceptional viral diversity compared to acute infections. This has lead to suggestions that immunocompromised individuals with chronic NoV infections could act as reservoirs for the emergence of novel variants. Despite this, very little is known about what, if any, contribution these viruses make, as a source population, to global epidemics or any sustained transmission in the community.

Method
In this study, we examine the viral diversity and patterns of evolution of a chronic NoV infection in an immunocompromised host over a 3-year period by next-generation sequencing.

Result
Throughout the infection, a highly heterogeneous viral intra-host population was maintained with 10-17 distinct haplotypes (frequency >1%) identified at each sampling point. Remarkably, the rate of evolution in the viral capsid gene within this individual was an order of magnitude higher (7.34 x 10-2 subs/site/year) than the estimated global GII.4 capsid substitution rate (4.3 x 10-3 subs/site/year). In agreement with our data, high rates of evolution were also observed in three other chronic NoV infections where similar longitudinal data was available (range 1.85-2.66 x 10-2 subs/site/year). Additional analyses for evidence for positive selection may indicate host-driven viral adaptation despite the compromised immune status of the individual.

Conclusion
Finally, we discuss factors that may contribute to the elevated rates of evolution including positive selection and transmission bottlenecks, as well as, the role these chronic infections play in the global dynamics of NoV infections.