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Norovirus (NoV) infections are the most common cause of acute nonbacterial gastroenteritis worldwide, and pose significant economic health burdens. Even after symptomatic infection resolves, shedding of infectious virus can persist for weeks in healthy hosts and months in immunocompromised hosts. Viral mutation in these immunocompromised hosts may allow for emergence of more pathogenic variants. Strains of Murine Norovirus (MNoV) also persist, providing a useful murine model for NoV infection. We study two strains of MNoV—CW3, which infects acutely, and CR6, which infects persistently. We seek to understand how viral evolution is regulated by the immune system, and whether immunocompromised hosts and/or immunoprivileged tissue sites alter viral evolution. Additionally, we hypothesize that acute viral strain CW3 was originally derived from mutation of persistent strain, such as CR6, in an immunocompromised host. We report that intracranial inoculation and passaging of a persistent MNoV strain in *Stat1-/-* mice lead to significant phenotypic shifts, including loss of persistence and the development of lethality after oral inoculation. Using Nextera sequencing methods, we have been performing deep sequencing of the MNoV viral genome in order to identify viral genotypic changes in the ssRNA genome that correlate with these phenotypic shifts. The identification of critical residues in the MNoV genome will help us to understand how pathogens mutate in immunocompromised hosts, and may provide key insight into viral evolution of human NoV.