

Highly Replicating Hepatitis C Variants Linked to Severe Liver Disease

A genetic switch drives rapid HCV replication in immunosuppressed patients, leading to more severe liver disease.

February 13, 2026 By [Sukanya Charuchandra](#)

Researchers have identified a viral switch that boosts [hepatitis C virus \(HCV\)](#) replication, particularly in immunocompromised transplant recipients, according to research published in [Nature Communications](#). Highly replicating virus was also found in people with HIV/HCV coinfection and [liver cancer](#). This transformation of viral fitness was linked to a more severe and potentially fatal form of liver disease.

HCV is usually present as a mixture of closely related but genetically distinct variants within a single individual. Typically, it is a slowly replicating virus, but it can evolve into a highly aggressive, fast-replicating form, especially in people with suppressed immune function. This genetic variation helps HCV evade the immune system, but exactly how it manifests is not well understood.

Volker Lohmann, PhD, of Heidelberg University in Germany, and colleagues sought to understand what makes certain HCV variants replicate faster, making them more successful. To investigate how HCV adapts to replicate more rapidly in certain patients, they used a combination of genetic sequencing, cell culture modeling and tissue analysis.

The researchers used samples of HCV collected at various time points from an individual who had received two liver transplants. Before the first transplant, the patient's blood revealed a diverse population of HCV variants, all of which showed low replication fitness, as is usual in chronic infection. But after the first transplant, the viral population became far more uniform, with one dominant variant that had a replication fitness over 50 times higher than its predecessors.

The team then essentially rebuilt versions of this virus in the lab to test which specific regions in the viral genome helped throttle or ramp up replication. They identified a specific region, which they named the Replication Enhancing Domain (ReED), within the NS5A segment of the viral genome, which is responsible for speedier viral replication. They found a slew of mutations in a particular stretch of the ReED.

The researchers noted that the ReED, when left alone, acts as a brake to slow down viral

replication and maintain chronic infection while keeping the virus hidden from the immune system. As this genetic region develops more mutations, the brake slips and viral replication explodes, particularly in immunocompromised individuals.

The team then extended their findings from this single transplant recipient to a cohort of 22 patients, some of whom developed a severe, fatal form of liver disease called fibrosing cholestatic hepatitis. This group carried only highly replicating HCV variants that had several mutations within the ReED region. Numerous liver cells tested positive for the virus, which damaged the liver with its massive onslaught.

“We identified high replication fitness as a general feature of HCV in fibrosing cholestatic hepatitis patients, arguing for a direct connection between the increase in viral replication and the severe course of disease,” wrote the researchers.

The scientists also found that these aggressive, highly replicating HCV variants in other immunocompromised groups, people with a HIV/HCV coinfection and patients with hepatocellular carcinoma, the most common type of liver cancer).

“[W]e observed that sequence signatures of high replication fitness are rare in immunocompetent patients but found more frequently in the context of profound immunosuppression, such as occurs at the early stages of transplantation, indicating a complex interplay between viral replication fitness and the host immune response,” the researchers noted.

Reassuringly, however, the team found that existing direct-acting antiviral drug seem to be effective against these aggressive HCV variants.

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