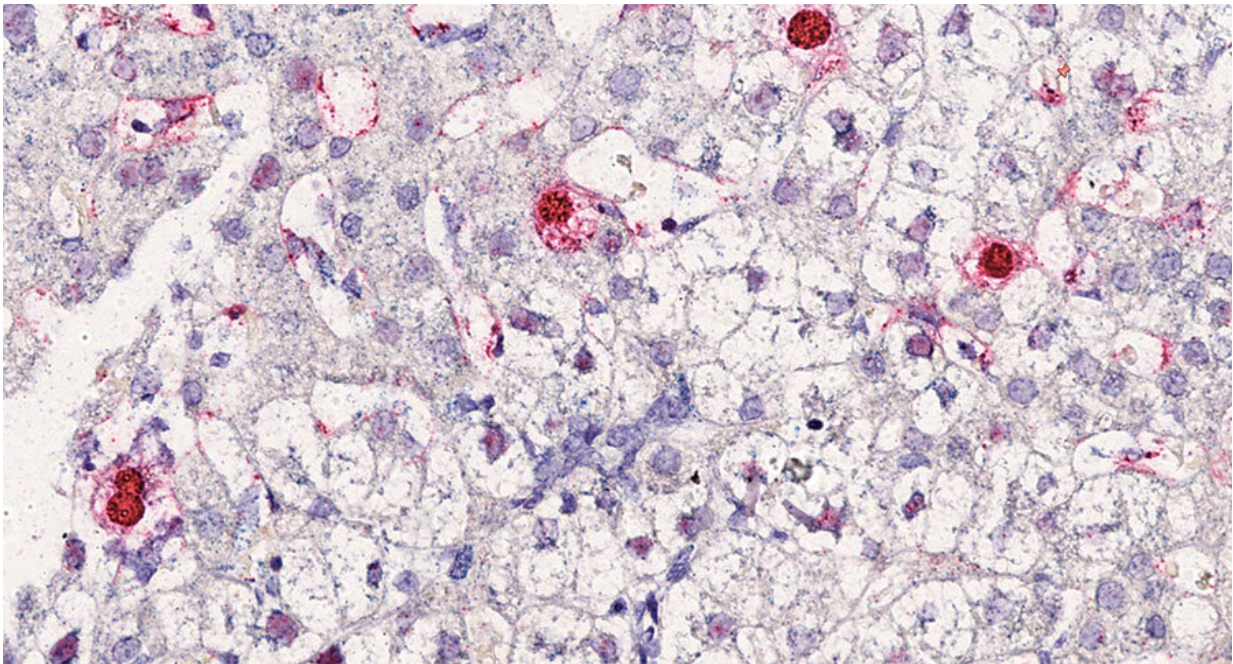


Discovery of a circovirus involved in human hepatitis

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In situ hybridization in liver section from a heart-lung transplant patient in France. Chromogenic in situ hybridization detected human circovirus type 1 mRNA (red staining) in hepatocytes nuclei and cytoplasm. Nuclei were counterstained with Harris hematoxylin and eosin stain; original magnification $\times 40$. Credit: *Emerging Infectious Diseases* (2023). DOI: 10.3201/eid2902.221468

Scientists from the Institut Pasteur, Necker-Enfants Malades Hospital (AP-HP), Inserm in the Imagine Institute, Université Paris Cité and the Alfort National Veterinary School (EnvA) have identified a previously

unknown species of circovirus, provisionally named human circovirus 1 (HCirV-1).

Circoviruses are a family of small, highly resistant DNA viruses that were initially identified in 1974 in various animal species, where they can cause respiratory, renal, dermatological and reproductive problems. HCirV-1 is a novel virus that is distant from known animal circoviruses. It was shown to be implicated in damage to the liver of a patient undergoing immunosuppressive treatment. This discovery of the first circovirus in humans, linked to hepatitis, was published in *Emerging Infectious Diseases*.

Although the transmission of animal viruses to humans is regularly reported in the scientific literature, it is rare for a novel virus to be identified in a patient in Europe. But as part of a recent study, scientists and physicians have identified the first circovirus involved in human hepatitis.

"The patient had unexplained chronic hepatitis, with few symptoms. She had received a heart-lung transplant 17 years earlier and had been monitored regularly since. We had access to a large number of samples over several years and were therefore able to identify this novel virus, which was completely unexpected," explains Marc Eloit, last author of the study, Head of the Institut Pasteur's Pathogen Discovery laboratory and a Professor of Virology at the Alfort National Veterinary School (EnvA).

His laboratory specializes in the identification of pathogens in patients suspected of severe infection of unknown cause.

In March 2022, in collaboration with the Department of Clinical Microbiology at Necker-Enfants Malades Hospital (AP-HP), the pathological tissue samples of this 61-year-old female patient receiving

immunosuppressive treatment, whose hepatitis had no identifiable cause, were sequenced to search for microbial sequences. The RNA (ribonucleic acid) sequences extracted from the tissues were analyzed and compared with those of known microbes.

"The aim is to identify sequences of interest among all the sequences obtained, which is like searching for a needle in a haystack," continues the scientist Marc Eloit. These thousands of RNA sequences were analyzed in parallel using mNGS (metagenomic next-generation sequencing) high-throughput sequencing techniques and sophisticated algorithms. After ruling out common etiologies, the analysis led to the identification of a previously unknown species of circovirus, provisionally named human circovirus 1 (HCirV-1). No other viral or bacterial sequence was found.

The involvement of HCirV-1 in the hepatitis was then demonstrated by analyzing samples taken from the patient in previous years as part of her post-transplant treatment. The results showed that the HCirV-1 [viral genome](#) was undetectable in the blood samples from 2017 to 2019, then that its concentration peaked in September 2021. Viral replication in [liver cells](#) was demonstrated (2 to 3% of liver cells were infected), pointing to the role of HCirV-1 in liver damage: once the virus has used the resources in the liver cell to replicate, it destroys the cell.

From November 2021 onwards, following antiviral treatment, the patient's liver enzymes returned to normal levels, indicating the end of hepatic cytolysis.

Diagnosing hepatitis of unknown etiology remains a major challenge, as shown by the cases of acute hepatitis reported in children in the United Kingdom and Ireland last April and signaled by WHO.

"We need to know the cause of the hepatitis, and especially whether or

not it is viral, to be able to offer suitable treatment and monitor patients effectively. The identification of this [novel virus](#) that is pathogenic in humans, and the development of a test that can be performed by any hospital laboratory, offers a new tool for diagnosing and monitoring patients with hepatitis," stresses Anne Jamet from the Department of Clinical Microbiology at Necker-Enfants Malades Hospital (AP-HP), who is also affiliated with Inserm and co-last author of the study.

Although some circoviruses are pathogenic for animals and vaccines can be administered, especially in pigs, this is the first known circovirus to be pathogenic for humans. The patient's symptoms remained mild; the virus was able to be identified because she was being closely monitored following her combined transplant.

The origin of the virus—whether it is circulating in humans or of animal origin—has yet to be identified, and the source of infection (contact, food, etc.) remains unknown. Following their discovery, the scientists developed a specific PCR test that is now available for etiological diagnosis of hepatitis of unknown origin. A serological test is also being developed.

"These results show the value of this type of sequencing analysis in identifying novel or unexpected pathogens. It is always important for clinicians to know whether or not an infection is viral so that they can adapt the treatment accordingly. It is also crucial to be able to identify a novel pathogen when an infection remains unexplained and to develop a diagnostic test, because any new case of human infection with an emerging pathogen may potentially signal the start of an outbreak," concludes Marc Eloit. The test is available for the medical community and can now be easily performed for other cases of unexplained hepatitis.

More information: Philippe Pérot et al, Circovirus Hepatitis Infection

in Heart-Lung Transplant Patient, France, *Emerging Infectious Diseases* (2023). [DOI: 10.3201/eid2902.221468](https://doi.org/10.3201/eid2902.221468)

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