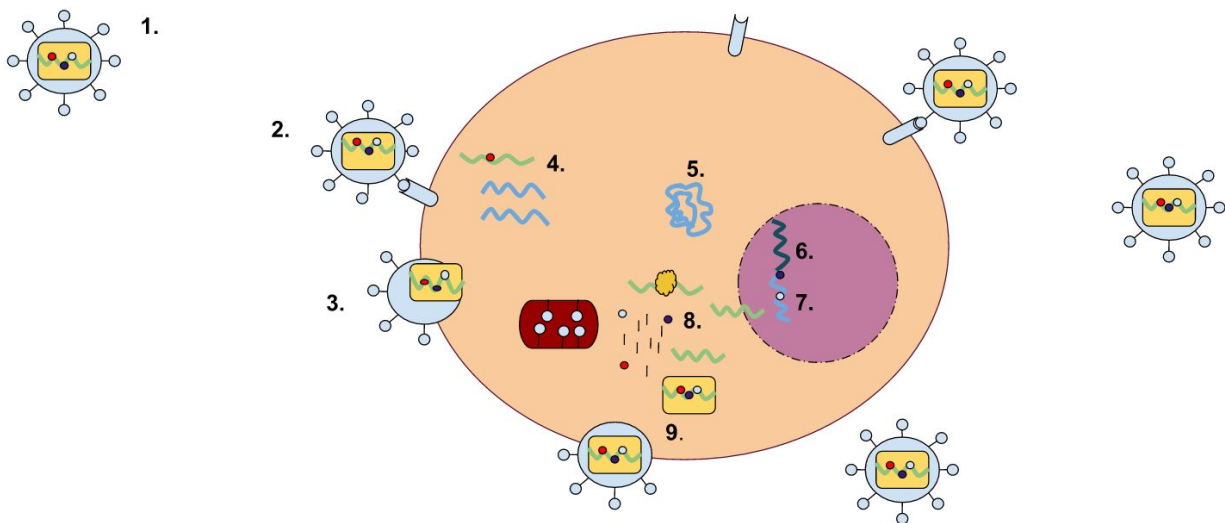


Evidence that addictive behaviors have strong links with ancient retroviral infection

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A retrovirus has a membrane containing glycoproteins, which are able to bind to a receptor protein on a host cell. There are two strands of RNA within the cell that have three enzymes: protease, reverse transcriptase, and integrase (1). The first step of replication is the binding of the glycoprotein to the receptor protein (2). Once these have been bound, the cell membrane degrades, becoming part of the host cell, and the RNA strands and enzymes enter the cell (3). Within the cell, reverse transcriptase creates a complementary strand of DNA from the retrovirus RNA and the RNA is degraded; this strand of DNA is known as cDNA (4). The cDNA is then replicated, and the two strands form a weak bond and enter the nucleus (5). Once in the nucleus, the DNA is integrated into the host cell's DNA with the help of integrase (6). This cell can either stay dormant, or RNA may be synthesized from the DNA and used to create the proteins for a

new retrovirus (7). Ribosome units are used to transcribe the mRNA of the virus into the amino acid sequences which can be made into proteins in the rough endoplasmic reticulum. This step will also make viral enzymes and capsid proteins (8). Viral RNA will be made in the nucleus. These pieces are then gathered together and are pinched off of the cell membrane as a new retrovirus (9). Credit: Wikipedia/CC BY-SA 3.0

New research from an international team led by Oxford University's Department of Zoology and the National-Kapodistrian University of Athens, published today in *Proceedings of the National Academy of Sciences (PNAS)*, shows that an ancient retrovirus—HK2—is more frequently found in drug addicts and thus is significantly associated with addiction.

The human genome is "littered" with remnants of ancient retrovirus infections that invaded the germline of our primate ancestors. Only one of these may still be proliferating in [modern humans](#) named HERV-K HML-2 (HK2), and not all humans have the same HK2 viruses in their genomes. One specific uncommon HK2, which lies close to a gene involved in dopaminergic activity in the brain (RASGRF2), is more frequently found in [drug addicts](#) and thus is significantly associated with addiction.

The Oxford University and University of Athens research teams have shown that HK2 can manipulate nearby genes. Their study provides strong evidence that uncommon HK2 integrations can be responsible for the unappreciated pathogenic burden of addictive behaviours.

The team analysed samples of Hepatitis C Virus (HCV)-infected patients from the UK and HIV-infected patients from Greece who had become infected according to distinct, known routes of infection (injecting

drugs), to determine the frequency of the HK2 integration in individuals. The particular HK2 insertion in the RASGRF2 gene is usually prevalent in 5-10% of the population.

This study shows that people with well-defined addictive behaviour i.e. Persons Who Inject Drugs (PWID) are 2 to 3 times more likely to have the integration of HK2 within RASGRF2 (a gene involved in regulating dopaminergic activity in the brain). It is thus a strong indication that HK2 within RASGRF2 predisposes these people in addictive behaviour.

Professor Katzourakis, from the University of Oxford, who co-directed the study said: 'We know of clear biological roles for a small number of human endogenous retroviruses. However, there has never before been strong evidence in support of a role in human biology of an endogenous retrovirus that is unfixed, in other words not shared by all individuals in the population. Our study shows for the first time that rare variants of HK2 can affect a complex human trait. The replication of this finding in the distinct Athens and Glasgow cohorts is particularly important.'

Dr. Magiorkinis, from the University of Athens, who led the study added: 'Most people think these ancient viruses are harmless. From time to time, people have shown overexpression of HK2 in cancer, but it has been difficult to distinguish cause from effect. Back in 2012, following a 20-year controversy regarding their pathogenic roles in humans, we sought to test the high-risk hypothesis that HERVs can be responsible for human disease. Our proposal was supported by the Medical Research Council, and now we have strong proof that HERVs can be pathogenic. For the first time, we are able to make a distinction between cause and effect in HERV pathogenicity.'

The integration of the [virus](#) predates the emergence of modern humans, as it has been found in Neanderthal and Denisovan genomes, and therefore it is not the behaviour of PWIDs that determines the presence

of the virus. Rather, it is likely that the virus is associated with addictive behaviour. Not all PWIDs carry this virus so there will be many other genetic and behavioural factors involved, but this is an important predictive factor in addiction. Furthermore the researchers' experimental work supports a causal role in the expression of RASGRF2 and hence addiction.

By providing support for a strong genetic predisposition of addictive behaviour, the Oxford research team advocates in support of medical-pharmacological interventions in support of addicts. Their study shows that new sequencing technologies and large genomic projects such as the 100,000 genomes project will deliver enhanced understanding of genetic features that were previously not well-understood.

Dr. Magiorkinis said: 'Looking into this "dark" part of the genome will unlock more genomic secrets.'

Most HERVs in the genome are shared by most human individuals. So if you pick two random people and check to see if they have the same HERVs in the same genomic location, it will be there. This is not true of some copies of HK2; there is variation, with certain individuals carrying extra copies in their genomes at distinct locations. Amazingly, it appears there are some rare variants where the integrated virus is 'coding competent'. In other words, it is an unbroken blueprint that could be used to make more viruses which could be active and cause problems to the human host.

HERVs carry signals to manipulate the host's replication machinery, and they do this for their own selfish purposes—to increase their copy number at the expense of the host. However, if they integrate near a gene, these same signals will affect the expression and function of the gene near which they have integrated. While researchers still have gaps in their understanding of how exactly this happens, the experiments of

this research team show that by inserting HK2 within a gene the transcription of the gene was significantly altered.

Since the discovery of HIV and (Human T-Lymphotropic Virus) HTLV, this is the third case in which a human retrovirus has been strongly linked with a harmful effect in humans. In this case, the harmful effect that researchers have identified is a complex behavioural condition. It could be said that this virus is 'conditionally pathogenic' as many individuals could carry it and not suffer negative consequences.

HIV spreads between individuals; differences in prevalence of HK2 are largely heritable, although it is possible that some HK2 viruses could still be infectious in the human populations. A very promising area of future research are the interactions between HK2 and other infectious human viruses. It is notable that the two cohorts of PWIDs that the researchers investigated are chronically infected with HIV and HCV respectively.

The researchers hope that by understanding the mechanistic-biochemical features of [addictive behaviour](#) better pharmacological targets can be developed for drug development. And as HK2 (the predictive factor) is a [retrovirus](#) it is possible that existing drugs could be used as starting points for research into this area.

More information: Timokratis Karamitros et al., "Human Endogenous Retrovirus-K HML-2 integration within RASGRF2 is associated with intravenous drug abuse and modulates transcription in a cell-line model," *PNAS* (2018). www.pnas.org/cgi/doi/10.1073/pnas.1811940115

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