

THE VIRUSES THAT MADE US

VIRUSES GIVE US INFECTIONS, FROM THE COMMON COLD TO EBOLA AND AIDS. BUT NEW RESEARCH SHOWS THAT THEY MAY ALSO HAVE PLAYED A KEY ROLE IN SHAPING THE EVOLUTION OF *HOMO SAPIENS*

WORDS: KAT ARNEY

Zika, Ebola, flu, even the boring old common cold – we’re all familiar with the viruses that plague humanity. But while we know they make us sick, it may be surprising to discover that, over millions of years, we’ve managed to harness and domesticate these crafty invaders. From the earliest stages of life to the smiles on our faces, viruses have had a huge influence on our human species. Viruses are little more than a string of genes (usually in the form of a molecule called RNA) packaged in a protein coat, and they all work in the same basic way. Once a virus has infected a cell, it hijacks the cell’s own molecular machinery to copy its genes and churn out viral proteins. New viruses are assembled from these freshly manufactured parts, which eventually burst out in search of new cells to attack [see box on p52]. For most viruses, such as flu, the story ends there. But a handful of retroviruses – including HIV – are even

sneakier, smuggling their way into our DNA. They insert themselves randomly into the genome of an organism, lying low until the time is right to start virus production again. But once a retrovirus has got into an organism’s DNA, there’s no guarantee that it will stay put. The genetic instructions can be ‘read’ from the embedded virus, converted into DNA and then pasted into another location in the genome. Repeat this cycle again and again, and multiple copies of the viral DNA quickly build up. Over millions of years, these viral DNA sequences randomly mutate and change, losing their ability to break free from their host cells. Trapped inside the genome, some of these ‘endogenous’ retroviruses can still jump around while others are stuck forever where they last landed. And if any of these events happen in the germ cells that make eggs and sperm, then they will be passed down the generations and eventually become a permanent part of an organism’s genome. ●

ILLUSTRATION: CHARIS TSEVIS

BBC RADIO
5 live
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HUMAN

● Around half of the human genome is made up of millions of DNA sequences that can be traced back to long-dead viruses or similar ‘jumping genes’, known collectively as transposable elements or transposons. Some researchers would even put this figure up at 80 per cent, as ancient sequences are now degraded beyond the point of being recognisably virus-like, weathered within the genome like molecular fossils.

For many years, the large chunks of repetitive virus-derived DNA littering the human genome were dismissed as ‘junk’. A proportion of this repetitive stuff undoubtedly *is* little more than junk in our genetic trunk, but as researchers look more closely at individual viral elements, a more sophisticated picture is emerging. And it turns out that as well as being our genetic enemies, some of the viruses embedded in our genome have become our slaves.

MAKING MAMMALS

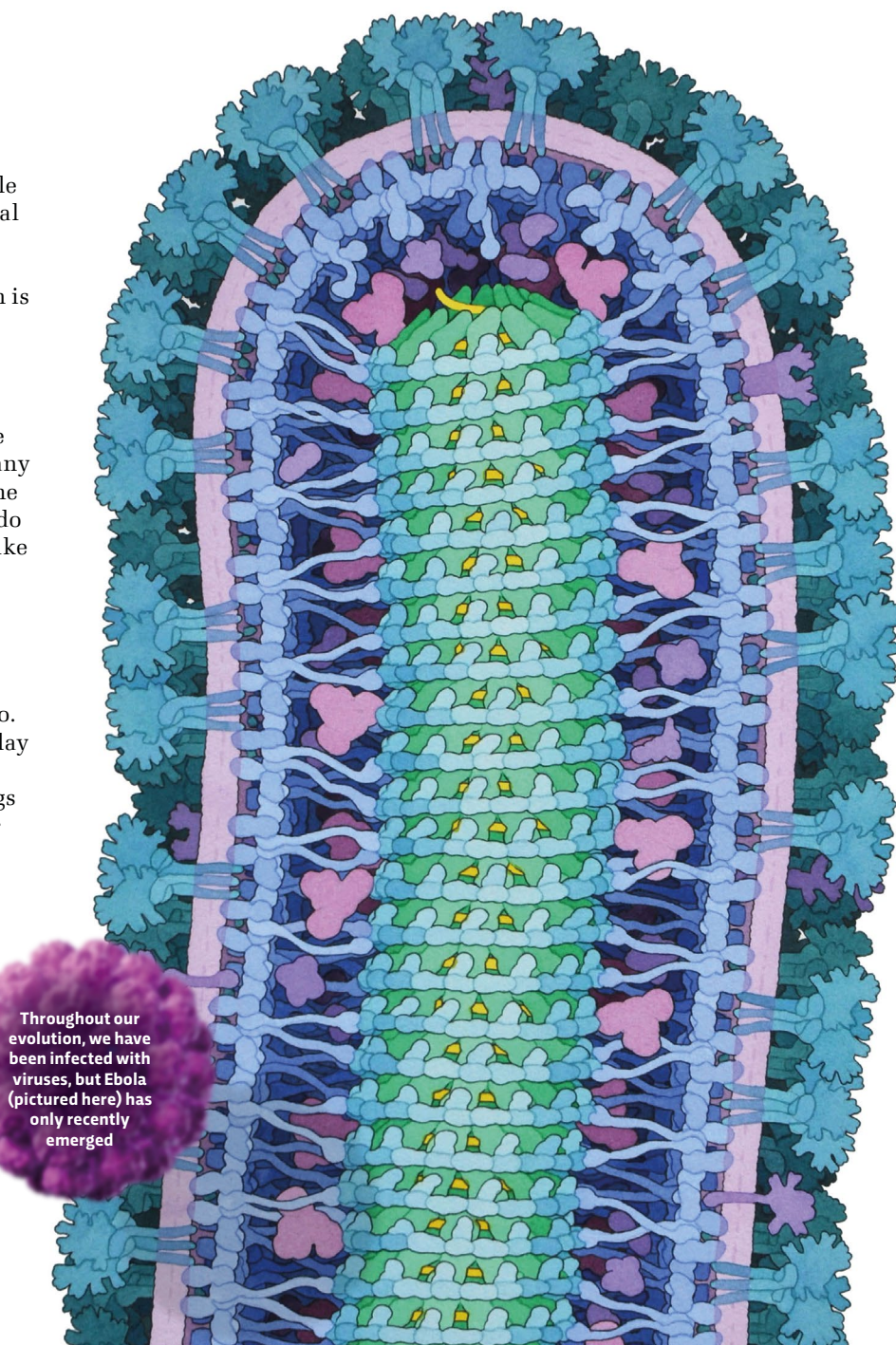
Around 15 years ago, US researchers discovered a human gene that was only active in the placenta. They called it syncitin, because it makes a molecule that fuses placental cells together, creating a special layer of tissue known as a syncytium. Curiously, syncitin looks a lot like a gene from a retrovirus. Another syncitin gene was later discovered, which is also involved in forming the placenta as well as preventing the mother’s immune system from attacking the foetus in her womb. Again, the gene looks like it has come from a retrovirus.

But while humans and other large primates have the same two syncitin genes, they aren’t found in any other mammals with similar fused cell layers in the placenta. Mice also have two syncitin genes: they do the same job as the human version, but they look like completely different viruses. And there’s another separate virally-derived syncitin gene in cats and dogs, both of which are descended from the same carnivorous ancestors.

Clearly, all these mammalian species were infected by particular viruses millions of years ago. Over time, those viruses have been harnessed to play a key role in placental growth, making them a permanent fixture in our genome. Intriguingly, pigs and horses don’t have a layer of fused cells in their placenta, and they also don’t have any genes that look like virally-derived syncitins. So maybe they never caught one of these fusing viruses.

While the case of syncitin reveals the wholesale adoption of a virus gene to do our bidding, there are many more examples of how ancient viral sequences can influence gene activity in today’s humans. Back in the 1950s, painstakingly detailed work by the long-overlooked American geneticist Barbara McClintock revealed that ‘jumping genes’ could affect the genome of maize plants. And just like the ‘jumping genes’

“AS WELL AS BEING OUR GENETIC ENEMIES, SOME OF THE VIRUSES EMBEDDED IN OUR GENOME HAVE BECOME OUR SLAVES”



Throughout our evolution, we have been infected with viruses, but Ebola (pictured here) has only recently emerged

McClintock identified in maize, the endogenous retroviruses that lurk in our own human genome have been on the move over millions of years, jumping around at random and altering the activity of genes in their immediate vicinity.

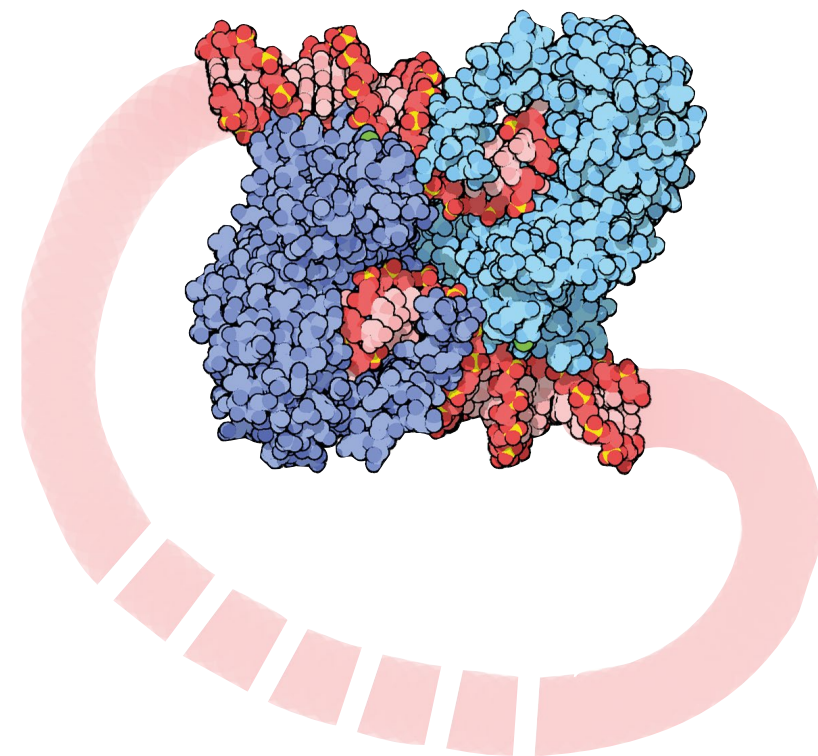
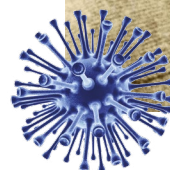
Our cells invest a lot of energy in attempting to stop these viral elements from going on the hop. They’re labelled and locked down with chemical tags, known as epigenetic marks. But, as the viral elements move, these molecular silencers move with them, so the viral sequences’ effects can spread to neighbouring genes wherever they land.

Conversely, viruses are also full of DNA sequences that attract molecules which switch genes on. In a functional retrovirus, these ‘switches’ activate the viral genes so it can become infectious again. But when a virus-like sequence gets spliced into another region in the genome, this ability to act as a genetic switch can end up going rogue.

In 2016, scientists at the University of Utah found that an endogenous retrovirus in the human genome – which originally came from a virus that infected our ancestors roughly 45 million to 60 million years ago – switches on a gene called AIM2 when it detects a molecule called interferon, which is the ‘danger signal’ that warns the body that it’s suffering a viral infection. AIM2 then forces the infected cells to self-destruct, to prevent the infection from spreading



PHOTOS: DAVID S GOODELL/RCSP PROTEIN DATA BANK X2, GETTY X2, ALAMY



ABOVE RIGHT: Two molecules of the ‘cut and paste’ enzyme transposase (blue and purple) grip onto the free ends of a DNA transposon (pink), ready to insert it into a new site within the genome

BELOW LEFT: Barbara McClintock first identified the effects of ‘jumping genes’ in maize

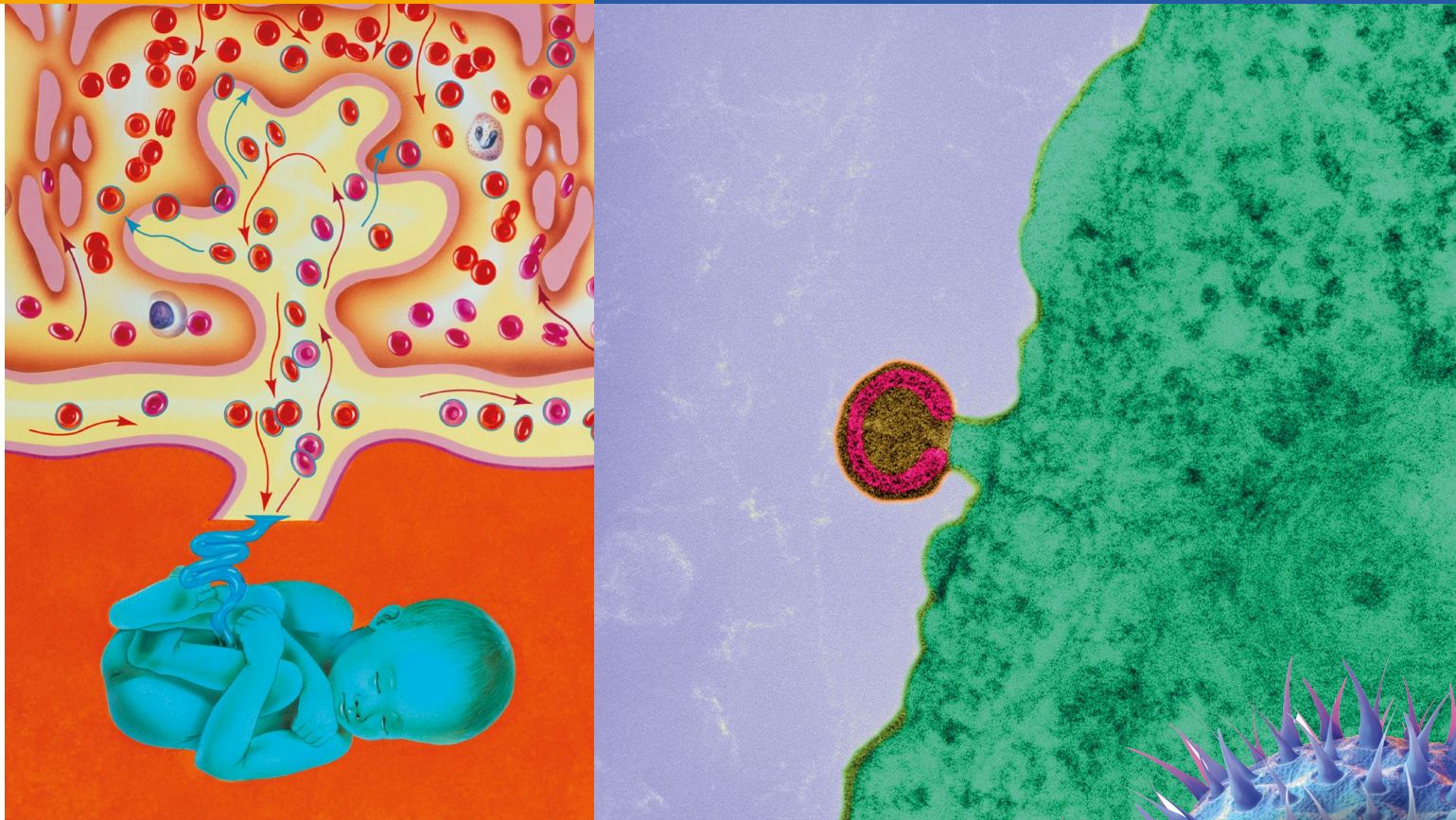
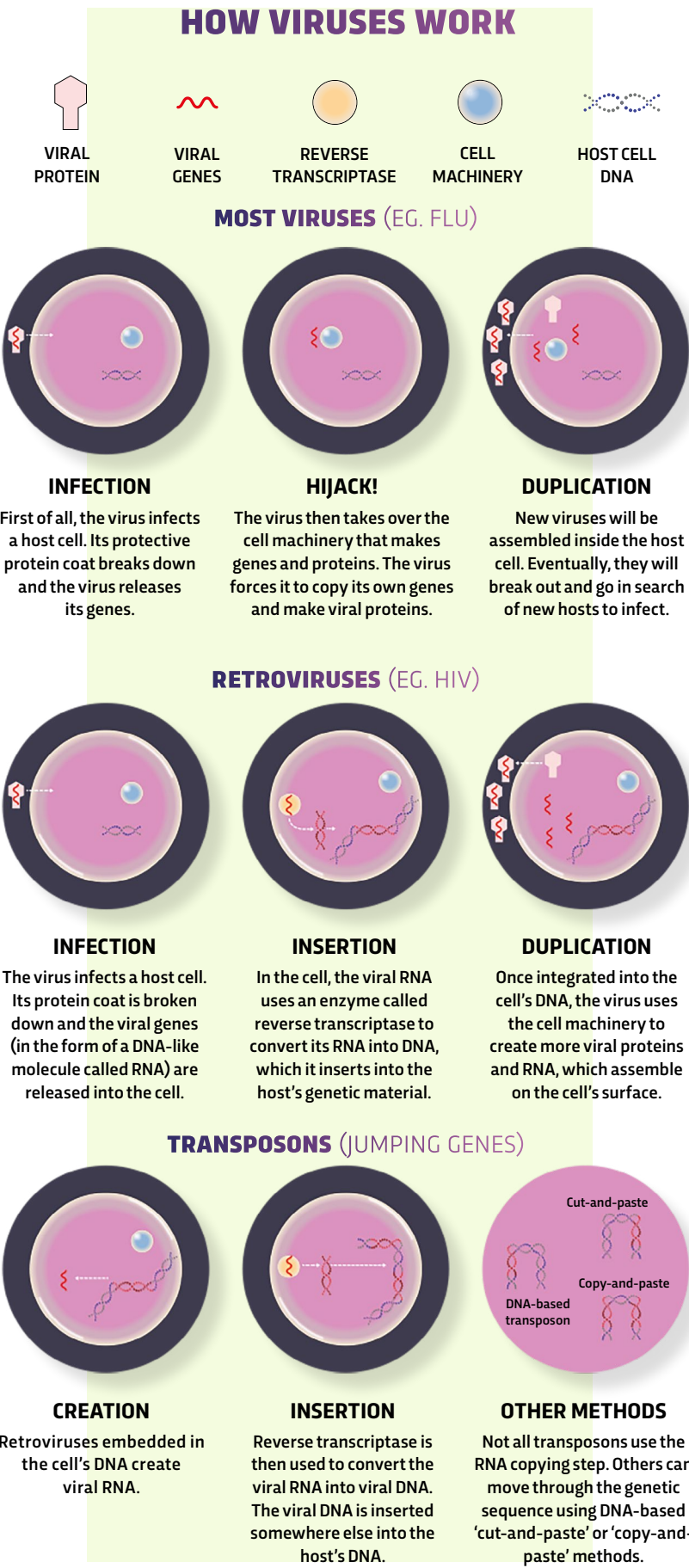
any further. These ancient viruses have become ‘double agents’, helping our cells to tackle other viruses that are trying to attack us.

Another example of a virus that may have shaped our species is found near a gene called PRODH. PRODH is found in our brain cells, particularly in the hippocampus. In humans, the gene is activated by a control switch made from a long-dead retrovirus. Chimpanzees also have a version of the PRODH gene, but it’s not nearly so active in their brains. One possible explanation is that an ancient virus hopped a copy of itself next to PRODH in one of our long-dead ancestors, millions of years ago, but that this didn’t happen in the ancestral primates that went on to evolve into today’s chimps. Today, faults in PRODH are thought to be involved in certain brain disorders, so it’s highly likely to have had at least some kind of influence on the wiring of human brains.

Similarly, variations in genetic switches are responsible for the differences between the cells that build our human faces as we grow in the womb and those of chimps. Although our genes are virtually identical to chimpanzee genes, we certainly don’t look the same. So the difference must lie in the control switches. Judging by their DNA sequences, many of the switches that are active in the cells that grow our faces seem to have originally come from viruses, which must have hopped into place sometime in our evolutionary journey towards becoming the flat-faced species we are today.

THE VIRUS TAMERS

As well as searching for examples of long-dead viruses that have altered our biology, scientists are searching for the control mechanisms that ●



underpin their effects. The key culprits are special silencing molecules called KRAB Zinc Finger Proteins (KRAB ZFPs), which grab hold of viral sequences in the genome and pin them in place. Prof Didier Trono and his team at the University of Lausanne in Switzerland have discovered more than 300 different KRAB ZFPs in the human genome, each of which seems to prefer a different virally-derived DNA target. Once there, they help to recruit the molecular machinery that turns genes on or off.

“These KRAB ZFPs have been viewed as ‘killers’ of these endogenous retroviruses,” Trono explains. “But they are actually exploiters of these elements that allow the organism to exploit the wealth of possibility that resides in these viral sequences.”

Trono and his team believe that KRAB ZFPs are the missing link between viral sequences that are actively harmful and those that have become tamed control switches. They have evidence that the proteins have evolved alongside the viral elements in a kind of ‘arms race’, initially suppressing them but eventually overpowering them.

“We think that what they do is domesticate these elements,” Trono says. “And by domestication, I mean not just making sure that the viruses stay put, but turning them into something beneficial for the host, which is a very refined way of regulating gene activity in all possible cells and situations.”

Supporting this idea is the finding that distinct groups of KRAB ZFPs are active in different types of cells. They’re also found in

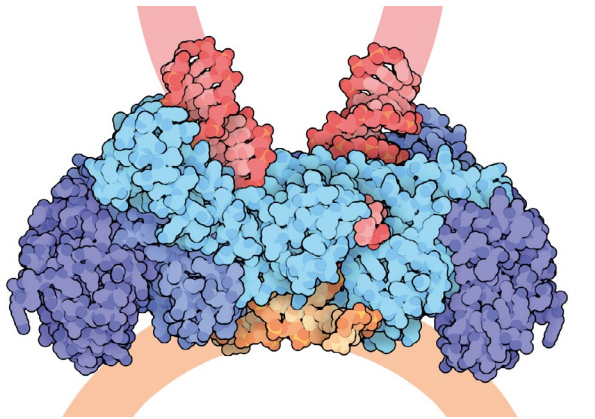
specific patterns in different species. If they were just suppressing viruses, the argument goes, the same array of proteins should be present in all cells. What’s more, why would they be found bound to the many thousands of long-dead viral elements that Trono and his team have identified? There’s no point suppressing a dead retrovirus, so they must be playing an important role in controlling gene activity.

Although his idea is still a little controversial, Trono sees the KRAB ZFPs as a force of viral slavedrivers, harnessing these elements to do our bidding and turning them into genetic control switches. Over many millions of years, this could have been a powerful motor for creating new species. For example, if a virus randomly goes on the hop in one ancestral creature and not another and is then tamed over time by a KRAB ZFP, it will create new control switches that could have a big impact on an animal’s appearance or behaviour.

What’s more, these jumping elements become more active during times of environmental change. As times get tough, species need to find new ways to adapt or they will die out. Activating these mobile elements reshuffles the genome, throwing up novel genetic variations that provide rich fodder for natural selection to work on.

FRIEND OR FOE?

It’s clear that the viruses trapped in our genome have brought us enormous benefits on an evolutionary



timescale. But they aren’t all so helpful. Around one in 20 human babies is born with a new viral ‘jump’ somewhere in its genome, which could deactivate an important gene and cause disease. There’s

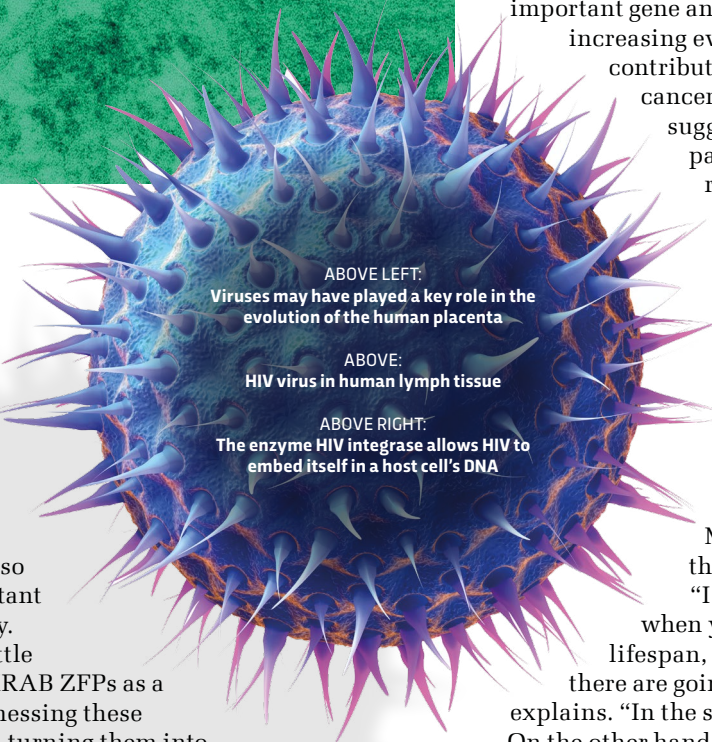
increasing evidence that jumping transposons contribute to the genetic chaos inside cancer cells. And intriguing research suggests that brain cells are particularly good locations for reactivating jumping genes, possibly increasing the diversity of nerve cells and enhancing our brainpower but also potentially causing ageing-related memory problems and conditions such as schizophrenia.

So are these viruses inside our DNA our friends or our enemies? Paolo Mita, a postdoctoral fellow researching transposons at NYU School of Medicine in New York, suggests that it’s a bit of both.

“I call them our ‘frenemies’, because when you look at their role in one human lifespan, most likely if they are mobilised there are going to be negative effects,” he explains. “In the short term, they are our enemies. On the other hand, if you are looking across time, these elements are a powerful force of evolution and they are still active in our species today. Evolution is just the way that organisms respond to changes in the environment, and in this case they are definitely our friends because they have shaped how our genome works now.”

And are the viruses infecting us today, such as HIV, going to have an impact on our evolution in the future? “Of course! The answer is why not?” laughs Mita. “But it will be many generations until we can look back and say this evolution has happened. But you can see the remnants of previous arms races in the genome between the endogenous retroviruses and the host cells. It’s a continuous battle, and I don’t think it has ever stopped.”

Kat Arney is a science writer and broadcaster. She hosts BBC Radio 5 Live’s *The Naked Scientists* and is the author of *Herding Hemingway’s Cats: Understanding How Our Genes Work*.



ABOVE LEFT: Viruses may have played a key role in the evolution of the human placenta

ABOVE: HIV virus in human lymph tissue

ABOVE RIGHT: The enzyme HIV integrase allows HIV to embed itself in a host cell's DNA