

Viral Fossils and the Divergent Mind: How an Ancient Chimpanzee Retrovirus Silenced a Key Neurodevelopmental Gene

Abstract

For over half a century, evolutionary biologists have grappled with a foundational paradox in comparative genomics: how do humans (*Homo sapiens*) and chimpanzees (*Pan troglodytes*) exhibit such profound differences in neuroanatomy, cognitive capacity, and developmental trajectory while sharing nearly 99 percent of their protein-coding DNA sequences? Traditional explanations have largely focused on human-specific genetic acquisitions, such as gene duplications and accelerated non-coding regulatory regions. However, recent advances in long-read epigenomic sequencing and stem-cell-derived brain organoid modeling have illuminated the opposite side of the evolutionary coin: lineage-specific loss of gene expression in non-human primates driven by ancient infectious agents. A landmark study published in *Science Advances* by Patricia Gerdes, Johan Jakobsson, and colleagues at Lund University demonstrates how an ancient retroviral infection permanently rewired the transcriptional landscape of the chimpanzee brain. Roughly four to five million years ago, after the hominin and panin lineages diverged, an exogenous gammaretrovirus known as Pan troglodytes endogenous retrovirus 1 (PTERV1) swept through ancestral chimpanzee populations while completely sparing the human lineage. By integrating into the germline on chromosome 19 within the locus of the long non-coding RNA gene *LINC00662*, a single PTERV1 provirus triggered a host defensive epigenetic response. Through dense cytosine-phosphate-guanine (CpG) DNA methylation and local heterochromatin spreading, the chimpanzee cellular machinery silenced the invading viral element—and inadvertently switched off the adjacent *LINC00662* promoter. In humans, who lack PTERV1 integrations entirely, *LINC00662* remains unmethylated and highly active during early forebrain development, where it interacts with RNA-binding proteins to drive neuronal maturation and neurite outgrowth. This article explores the paleovirological history of PTERV1, the molecular mechanics of host-driven epigenetic silencing, and the experimental breakthroughs in

CRISPR-Cas9 gene editing and cerebral organoids that revealed how a prehistoric viral colonization helped shape the evolutionary divergence of primate brains.

1. Introduction: The Primate Paradox and the Non-Coding Genome

When Mary-Claire King and Allan Wilson published their classic comparative study of human and chimpanzee macromolecules in 1975, they reached a conclusion that continues to anchor evolutionary genetics: the structural proteins encoded by the two species are more than 98.5 percent identical. When the initial draft of the chimpanzee reference genome was completed three decades later, it confirmed that single-nucleotide substitutions within orthologous protein-coding exons account for a tiny fraction of the genomic divergence between *Homo sapiens* and *Pan troglodytes*. Yet the phenotypic chasm separating the two species—particularly within the central nervous system—is unmistakable. The human cerebral cortex is roughly three times larger than that of a chimpanzee, exhibits a markedly prolonged period of postnatal synaptogenesis and myelination, and contains complex associative neural networks that support recursive language and abstract reasoning.

If the building blocks of the cell—the proteins themselves—are nearly identical between humans and chimpanzees, then the divergence must reside in the blueprint that dictates when, where, and in what quantities those proteins are synthesized. Over the past two decades, comparative neurogenomics has shifted its focus from the coding exome (which comprises less than 2 percent of the human genome) to the vast expanse of the non-coding genome. Within this dark matter of the genome lie cis-regulatory elements, enhancers, insulators, long non-coding RNAs (lncRNAs), and transposable elements (TEs). Transposable elements, often colloquially termed "jumping genes," make up roughly 45 to 50 percent of the mammalian genome. Rather than acting merely as inert genomic parasites or evolutionary junk, TEs represent a massive, dynamic reservoir of regulatory sequences capable of rewiring gene expression networks over evolutionary timescales.

Among these mobile genetic elements, endogenous retroviruses (ERVs) occupy a uniquely influential position. ERVs are the genomic footprints of ancient exogenous retroviruses that succeeded in infecting the germ cells (sperm, ova, or early embryonic cells) of ancestral hosts millions of years ago. Once integrated into the nuclear DNA of a germ cell as a provirus, the viral sequence becomes Mendelian: it is inherited vertically from parent to offspring across generations. Over millions of years, most ERVs accumulate point mutations, insertions, and deletions, or undergo homologous recombination between their flanking sequences, rendering them incapable of producing infectious viral particles.

Yet an inability to replicate as a virus does not equate to biological silence. Because retroviruses rely on the host cell's transcriptional machinery to transcribe their own genomes during active infection, their flanking sequences—known as long terminal repeats (LTRs)—are packed with potent transcription factor binding sites, promoters, enhancers, and polyadenylation signals. Conversely, because active retrotransposition and viral transcription pose a severe mutagenic risk to host genome stability, mammalian cells have evolved sophisticated epigenetic surveillance systems designed to recognize viral DNA and lock it down inside tightly compacted, transcriptionally silent chromatin.

Until recently, studies investigating how structural genomic variants drove hominoid brain evolution focused heavily on genetic innovations gained along the human lineage—such as the human-specific gene duplications *NOTCH2NL* and *ARHGAP11B*, which promote the proliferation of basal radial glia in the developing neocortex. However, evolutionary divergence is a two-way street. Two lineages splitting from a common ancestor can diverge just as profoundly when one lineage loses the expression of a shared ancestral gene while the other retains it. In their 2026 *Science Advances* investigation, Patricia Gerdes, Ofelia Karlsson, Raquel Garza, Diahann A. M. Atacho, and colleagues under the direction of Johan Jakobsson at Lund University turned this paradigm on its head. By examining the chimpanzee genome through the lens of long-read epigenomics and stem-cell neurobiology, they demonstrated that an ancient retroviral wave that struck chimpanzees—but missed humans—epigenetically silenced a critical neurodevelopmental gene, *LINC00662*, thereby altering the trajectory of neuronal maturation between the two species.

2. Paleovirology of PTERV1: An Ancient Asymmetric Outbreak

To understand how a viral sequence came to regulate a chimpanzee brain gene while leaving the human genome untouched, one must look back to the Pliocene and late Miocene epochs, roughly four to six million years ago. Around this time, the hominin lineage (leading to modern humans) and the panin lineage (leading to modern chimpanzees and bonobos) were completing their evolutionary split in Africa. During this post-speciation window, ancestral populations of African great apes were exposed to an exogenous gammaretrovirus that modern geneticists designate as *Pan troglodytes* endogenous retrovirus 1, or PTERV1 (also referred to in earlier literature as CERV1).

When researchers first began comparing bacterial artificial chromosome (BAC) sequences and whole-genome assemblies between primates in the mid-2000s, PTERV1 immediately stood out as a striking anomaly in evolutionary genetics. In a seminal 2005 study led by Evan Eichler and colleagues, genomic screening revealed over 100 copies of PTERV1 scattered across the genome of the common chimpanzee (*Pan troglodytes*) and the bonobo (*Pan paniscus*), as well as scores of copies in the lowland gorilla (*Gorilla gorilla*) and Old World monkeys such as the rhesus macaque (*Macaca mulatta*) and olive baboon (*Papio anubis*). Yet when the researchers examined the human genome, they found exactly zero copies of PTERV1. Equally surprising, the virus was entirely absent from Asian apes, including the orangutan (*Pongo pygmaeus*) and siamang.

Furthermore, when geneticists compared the precise genomic integration sites of PTERV1 across chimpanzees, gorillas, and macaques, almost none of the insertion loci were orthologous (shared at the exact same chromosomal coordinates) between chimpanzees and gorillas. Only chimpanzees and bonobos shared identical insertion coordinates, as they diverged from one another much more recently (roughly 1.5 to 2 million years ago). This non-orthologous distribution provided definitive proof that PTERV1 was not inherited vertically from a common ancestor of humans, chimpanzees, and gorillas. Instead, PTERV1 spread horizontally as an exogenous infectious pathogen that independently infected and colonized the germlines of ancestral chimpanzees and gorillas after they had already diverged from the human lineage.

Why did this prehistoric viral sweep leave scores of permanent genetic scars in the genomes of our closest living relatives in Africa while leaving the human genome completely pristine? While geographical isolation or ecological separation during the Pliocene could theoretically play a role, molecular virologists have uncovered compelling evidence for an innate intracellular restriction barrier. Primate cells express a family of intrinsic antiviral restriction factors known as tripartite motif-containing proteins, chief among them TRIM5alpha. The TRIM5alpha protein acts as a cytoplasmic pattern-recognition receptor that binds directly to the hexameric protein lattice of incoming retroviral capsids moments after the virus enters the host cell. Upon binding, TRIM5alpha induces premature uncoating of the viral core and targets it for proteasomal degradation, blocking reverse transcription before the virus can ever reach the nucleus.

Crucially, TRIM5alpha has undergone intense positive selection throughout primate evolution, resulting in species-specific variations within its capsid-binding B30.2/SPRY domain. In 2007, paleovirologist Michael Emerman and his team reconstructed the ancestral core protein of PTERV1 and tested the ability of various primate TRIM5alpha orthologs to restrict it in vitro. They discovered that the human version of TRIM5alpha potently blocks PTERV1 infection. In evolutionary terms, ancestral hominins likely possessed or evolved a specific amino acid configuration in TRIM5alpha that rendered them highly resistant to PTERV1 colonization, shielding the human germline from the retroviral insertions that were simultaneously accumulating across the chromosomes of ancestral chimpanzees and gorillas.

Primate Species	Common Name	Approximate Divergence from Human Lineage	Presence of PTERV1 in Genome	Approximate Copy Number (Full-Length & Fragmented)	Shared Integration Sites with Chimpanzee
<i>Homo sapiens</i>	Modern Human	Reference Lineage ▾	Absent ▾	0	None ▾
<i>Pan troglodytes</i>	Common Chimpanzee	6 to 7 million years ago ▾	Present ▾	158 proviral elements (RetroTector screen)	Reference for Pan genus ▾
<i>Pan paniscus</i>	Bonobo	6 to 7 million years ago ▾	Present ▾	Comparable to <i>P. troglodytes</i>	High (including the LINC... ▾

Primate Species	Common Name	Approximate Divergence from Human Lineage	Presence of PTERV1 in Genome	Approximate Copy Number (Full-Length & Fragmented)	Shared Integration Sites with Chimpanzee
<i>Gorilla gorilla</i>	Western Lowland Gorilla	8 to 10 million years ago ▾	Present ▾	Over 80 copies	Virtually none (independen... ▾
<i>Pongo abelii</i>	Sumatran Orangutan	12 to 16 million years ago ▾	Absent ▾	0	None ▾
<i>Macaca mulatta</i>	Rhesus Macaque	25 to 30 million years ago ▾	Present ▾	Over 100 copies	Virtually none (independen... ▾

3. Genomic Architecture and Epigenetic Lockdown of PTERV1

To evaluate how these chimpanzee-specific viral insertions influence modern gene regulation, the Lund University team first needed an accurate, comprehensive map of PTERV1 elements across the chimpanzee genome. Standard genome annotation tools, such as RepeatMasker, frequently struggle with endogenous retroviruses because they fragment a single proviral integration into separate annotation entries for the flanking LTRs and the internal coding sequences. To overcome this limitation, Gerdes and colleagues deployed the specialized bioinformatics tool RetroTector to scan the high-quality chimpanzee reference genome assembly ([CLINT_PTRv2/panTro6](#)).

Their computational screen identified 158 distinct PTERV1 proviral elements distributed across the chimpanzee chromosomes. A canonical, full-length PTERV1 provirus spans roughly 7 to 10 kilobases (kb) in length, with the identified chimpanzee elements ranging from 2 kb (partially truncated or recombined copies) to 14 kb, averaging 7.5 kb overall. Structurally, a full-length PTERV1 element exhibits the classic organization of a simple retrovirus: it contains four core viral genes—*gag* (encoding structural capsid and matrix proteins), *pro* (protease), *pol* (reverse transcriptase and integrase), and *env* (surface envelope glycoproteins)—flanked on both the 5-prime and 3-prime ends by identical long terminal repeats (LTRs) measuring 400 to 600 base pairs each.

When the researchers mapped the exact locations of these 158 PTERV1 elements relative to host chimpanzee genes, a clear evolutionary pattern emerged. The vast majority of the surviving proviruses resided in intergenic regions—the vast stretches of DNA between

protein-coding or non-coding genes. Furthermore, among the minority of PTERV1 copies that had integrated directly inside host genes (almost exclusively within introns), there was a strong, statistically significant bias toward integration in the antisense orientation relative to the host gene's direction of transcription.

This orientation bias is a classic signature of purifying natural selection. When a retrovirus integrates into an intron in the sense orientation, its internal polyadenylation signals and splice sites are read by the host's RNA polymerase II during gene transcription, frequently causing premature transcript termination or aberrant exon splicing that destroys the host gene's function. Such deleterious insertions are rapidly purged from the population by natural selection. Antisense insertions, by contrast, are less likely to physically truncate the primary transcript during elongation—though, as the LINC00662 story demonstrates, they are far from transcriptionally neutral.

The Host Epigenetic Defense System

Even when an ERV lands in an intergenic region or in an antisense intronic orientation, the host cell cannot leave the viral sequence unguarded. If left in an open, euchromatic state, the transcription factor binding sites within the viral LTRs can recruit host RNA polymerase II, driving ectopic transcription of viral RNA or hijacking the expression of neighboring host genes. To prevent this, vertebrates deploy a specialized genome defense system centered on Krüppel-associated box domain zinc finger proteins (KRAB-ZFPs).

KRAB-ZFPs make up the largest family of transcriptional regulators in mammals, consisting of hundreds of proteins whose C-terminal zinc finger arrays evolve rapidly to recognize specific DNA sequence motifs within newly invading retroviruses and transposable elements. Once a specific KRAB-ZFP binds to a proviral sequence like PTERV1, its conserved N-terminal KRAB domain recruits a master epigenetic scaffold protein called TRIM28 (also known as KAP1). TRIM28, in turn, assembles a macromolecular silencing complex that includes the histone methyltransferase SETDB1 (which deposits repressive trimethylation marks on lysine 9 of histone H3, denoted H3K9me3), the nucleosome remodeling and deacetylase (NuRD) complex, and DNA methyltransferases (DNMTs).

During early embryonic development, this complex converts the viral DNA into dense, inaccessible heterochromatin and catalyzes the covalent addition of methyl groups to the 5-carbon position of cytosine rings within CpG dinucleotides. Once established, this dense CpG DNA methylation is stably maintained across somatic cell divisions by maintenance methyltransferases (such as DNMT1), locking the viral fossil in a permanent state of transcriptional silence.

Measuring DNA methylation across repetitive viral elements was historically nearly impossible using short-read sequencing technologies (such as Illumina bisulfite sequencing). Because the 158 copies of PTERV1 share highly similar sequences across 7.5 kilobases, 150-base-pair reads cannot be mapped uniquely to a specific chromosomal locus; the reads pile up ambiguously. Gerdes and her colleagues bypassed this hurdle by utilizing long-read DNA sequencing from Oxford Nanopore Technologies (ONT). Because ONT sequencing passes intact, native DNA molecules tens of kilobases long through biological nanopores, a single sequencing read can span an entire 7.5 kb PTERV1 provirus along with thousands of base pairs of unique flanking chimpanzee genomic DNA on either side. Furthermore, because methylated cytosines alter the electrical current resistance differently than unmethylated cytosines as the DNA strand ratchets through the pore, ONT sequencing directly reads native CpG methylation at single-base resolution without chemical bisulfite conversion.

Applying this long-read epigenomic profiling to chimpanzee induced pluripotent stem cells (iPSCs) and 15-day-old unguided neural organoids, the team discovered that nearly every single one of the 158 PTERV1 loci was heavily, uniformly blanketed in CpG DNA methylation. Because humans lack these 158 insertions entirely, each methylated PTERV1 provirus effectively acts as a chimpanzee-specific island of dense heterochromatin embedded within the primate genome.

4. Comparative Brain Organoids: Uncovering the Silencing of *LINC00662*

Having established that the chimpanzee genome carries 158 viral heterochromatin domains absent in humans, the researchers asked a pivotal question: do any of these methylated viral islands spill over into adjacent genomic territory and silence nearby host genes during brain development?

Addressing developmental questions in hominoids has historically been stymied by severe ethical and practical constraints; researchers obviously cannot harvest developing fetal brain tissue from chimpanzees to compare against human neurodevelopment. The development of induced pluripotent stem cell (iPSC) technology and three-dimensional neural organoids has revolutionized this field. By reprogramming somatic cells (such as skin fibroblasts or blood cells) from adult humans and chimpanzees back into an embryonic-like pluripotent state, scientists can coax these iPSCs in culture dishes to self-organize into three-dimensional cerebral organoids that faithfully recapitulate the molecular, cellular, and architectural milestones of the early developing fetal forebrain.

Gerdes and her colleagues optimized a highly standardized protocol to grow unguided neural organoids from two biological replicates each of human and chimpanzee iPSCs under near-identical culture conditions. At day 15 of differentiation, organoids from both species exhibited remarkably similar macroscopic morphology, growth rates, and internal tissue architecture. Immunohistochemical staining confirmed that both human and chimpanzee organoids formed classic neural rosettes—radially organized tubular structures that mimic the embryonic neural tube—expressing the foundational neural progenitor transcription factor PAX6 and the apical tight-junction protein ZO1. Single-nucleus RNA sequencing (snRNA-seq) at day 15 further verified that the cellular composition of the organoids was highly comparable between the two species, consisting predominantly of proliferating neural progenitor cells (NPCs) and early-born post-mitotic neurons.

With this validated, apples-to-apples developmental model in hand, the team cross-referenced the genomic coordinates of their 158 methylated PTERV1 insertions against the transcriptional profiles generated by their single-nucleus and bulk RNA

sequencing datasets. One locus on chromosome 19 immediately stood out for its dramatic, all-or-nothing transcriptional divergence: the gene encoding the long non-coding RNA LINC00662.

The Chromosome 19 Locus and Heterochromatin Spreading

In the human organoids, *LINC00662* was robustly expressed across both neural progenitor cells and maturing neurons. In the chimpanzee organoids, by contrast, expression of LINC00662 was completely undetectable—the gene was entirely silent. Expanding their analysis to previously published transcriptomic datasets from additional primate cell models, the researchers confirmed that LINC00662 is strongly expressed in human neuronal models, but silent in chimpanzee, bonobo, and rhesus macaque neural progenitor cells.

A detailed structural examination of the chromosome 19 locus revealed the culprit. In the chimpanzee genome, a full-length PTERV1 provirus had integrated directly inside the first intron of the *LINC00662* gene, oriented in the antisense direction relative to LINC00662 transcription, just downstream of the gene's transcriptional start site (TSS) and core promoter. Comparative genomic alignments showed that this exact intronic PTERV1 insertion is shared between common chimpanzees (*Pan troglodytes*) and bonobos (*Pan paniscus*), pinpointing the original germline infection to the ancestral *Pan* population between 1.5 and 5 million years ago—after the split from humans, but before chimpanzees and bonobos diverged from one another.

When the researchers examined their Oxford Nanopore long-read methylation profiles across the *LINC00662* locus in both species, the mechanism of silencing became unmistakable. In human iPSCs and neural organoids, which lack the viral insertion, the CpG island spanning the *LINC00662* promoter is completely unmethylated, maintaining an open, permissive chromatin state that allows transcription factors and RNA polymerase II to bind freely. In chimpanzee iPSCs and neural organoids, the intronic PTERV1 provirus is densely methylated. Crucially, this epigenetic lockdown did not stop at the borders of the viral LTRs. Instead, the repressive DNA methylation spread outward from the PTERV1 element into the surrounding host DNA, blanketing the adjacent LINC00662 promoter in

CpG methylation. In attempting to defend the genome against an intronic retrovirus, the chimpanzee epigenetic machinery had inadvertently silenced the host gene's promoter.

Genomic & Epigenetic Feature	Homo sapiens (Human)	Pan troglodytes (Chimpanzee)	Pan paniscus (Bonobo)	Functional Consequence
Intronic PTERV1 Insertion at <i>LINC00662</i> Locus	Absent (Ancestral state retained)	Present (Integrated in antisense orientation)	Present (Shared ancestral <i>Pan</i> integration)	Creates a lineage-specific structural variant (~7.5 kb) in <i>Pan</i> species.
Epigenetic Status of Viral Insertion	Not applicable	Densely methylated across CpG dinucleotides	Densely methylated (inferred from NPC silencing)	Forms a localized intronic heterochromatin domain.
Epigenetic Status of <i>LINC00662</i> Promoter	Unmethylated (Open euchromatin)	Heavily methylated via heterochromatin spreading	Repressed	Blocks transcription factor and RNA polymerase II recruitment in chimpanzees.
<i>LINC00662</i> Transcriptional Activity in Neural Organoids / NPCs	High expression across NPCs and early neurons	Completely silenced (Zero detectable expression)	Completely silenced in NPC models	Divergent availability of the <i>LINC00662</i> lncRNA scaffold during neurodevelopment.

5. Proving Causality: CRISPR-Cas9 Rescue and Perturbation Experiments

In evolutionary genomics, correlating a structural variant with a difference in gene expression between two species is relatively straightforward; proving that the variant *causes* the expression difference is far more challenging. Over five to six million years of independent evolution, the *LINC00662* promoter and its surrounding regulatory regions in chimpanzees could theoretically have accumulated single-nucleotide mutations that inactivated the promoter independently of the PTERV1 virus. Alternatively, chimpanzees might lack a specific trans-acting transcription factor required to turn the gene on.

To establish definitive cause and effect, Gerdes and colleagues turned to precision genome editing using CRISPR-Cas9. They designed pairs of single-guide RNAs (sgRNAs)

targeting the unique flanking chimpanzee genomic sequences immediately upstream and downstream of the intronic PTERV1 provirus inside LINC00662. By introducing these guide RNAs alongside the Cas9 endonuclease into chimpanzee iPSCs, the researchers physically excised the entire PTERV1 viral insertion from the chimpanzee chromosome, seamlessly stitching the host intron back together to recreate the ancestral, pre-infection genomic architecture found in humans.

The results of this viral excision experiment were unambiguous. When the PTERV1 insertion was surgically removed from the chimpanzee stem cells, the epigenetic repression lifted and LINC00662 expression switched back on. This rescue experiment proved two critical biological facts: first, that the chimpanzee *LINC00662* promoter and transcriptional machinery remain fully intact and functional after millions of years of dormancy; and second, that the presence of the PTERV1 sequence itself is actively and continuously required to maintain the epigenetic silencing of the gene in chimpanzee cells.

6. Molecular Function of *LINC00662* in Human Neurodevelopment

Having proven why LINC00662 is silent in chimpanzees, the Lund team next investigated what the active gene actually does in the developing human brain. *LINC00662* belongs to the expansive class of long intergenic non-coding RNAs—transcripts longer than 200 nucleotides that are capped, spliced, and polyadenylated just like messenger RNAs (mRNAs), yet lack a functional open reading frame and are never translated into protein by the ribosome.

While early genomic studies often dismissed lncRNAs as transcriptional noise, molecular cell biology over the past fifteen years has established that many lncRNAs function as versatile macromolecular scaffolds, decoys, or guides. Because RNA is a flexible, single-stranded polymer that folds into intricate secondary and tertiary three-dimensional structures (stem-loops, hairpins, and pseudoknots), a single lncRNA molecule can simultaneously bind multiple proteins, DNA sequences, or other RNAs, bringing specific molecular partners into close physical proximity within the nucleus or cytoplasm. Prior to

the Lund study, *LINC00662* had primarily caught the attention of oncologists, who noted that its aberrant overexpression in somatic tissues promotes cell proliferation and migration in several human cancers, including neuroblastoma, glioma, and lung cancer. Its normal physiological role in human embryonic development, however, remained virtually uncharted.

Proteomic Pulldowns: Identifying the Molecular Partners

To uncover the biochemical mechanism of *LINC00662* in human neural cells, the researchers performed RNA pulldown assays coupled with high-resolution liquid chromatography-tandem mass spectrometry (LC-MS/MS)—a proteomic dataset deposited with the ProteomeXchange Consortium (identifier PXD071764). By synthesizing biotinylated *LINC00662* RNA transcripts, incubating them with protein lysates extracted from human neural cells, and capturing the resulting ribonucleoprotein complexes with streptavidin beads, the team identified the exact repertoire of intracellular proteins that physically bind to *LINC00662*.

The mass spectrometry analysis revealed that *LINC00662* interacts selectively with a cohesive network of RNA-binding proteins (RBPs) heavily enriched for functions in mRNA splicing, RNA transport, cytoskeletal organization, and neuronal differentiation. Prominent among these protein partners were factors known to orchestrate the formation and extension of neurites—the dynamic cytoplasmic projections extending from the cell body of a young post-mitotic neuron that ultimately differentiate into signal-receiving dendrites and signal-transmitting axons. By acting as a physical scaffold or regulatory sponge for these RNA-binding proteins, *LINC00662* helps coordinate the post-transcriptional processing and localized translation of messenger RNAs required to build the neuronal cytoskeleton.

Loss-of-Function in Human Brain Organoids: CRISPR Interference

To observe how the loss of *LINC00662* alters cellular behavior in developing human brain tissue—effectively mimicking the chimpanzee condition inside a human genetic background—the researchers utilized CRISPR interference (CRISPRi). Unlike standard CRISPR-Cas9 editing, which cuts the DNA double helix to delete sequences, CRISPRi employs a catalytically dead Cas9 protein (dCas9) fused to a potent transcriptional

repressor domain (such as KRAB). Guided to the unmethylated *LINC00662* promoter in human iPSCs by specific guide RNAs, the dCas9-KRAB complex sterically blocks RNA polymerase II and deposits repressive chromatin marks, silencing *LINC00662* transcription without altering a single base pair of the underlying human DNA sequence. To ensure that any observed cellular phenotypes were not caused by off-target effects, the team performed parallel experiments using two completely independent guide RNAs targeting the *LINC00662* promoter.

The researchers then differentiated these *LINC00662*-suppressed human iPSCs into three-dimensional neural organoids alongside unedited human control cells and monitored their developmental trajectory over 30 days.

- **Early Proliferation Phase (Day 15):** At the 15-day mark, when the organoids consist mostly of dividing neural progenitor cells arranged in PAX6-positive neural rosettes, suppressing *LINC00662* produced minimal macroscopic differences. The organoids formed normally, grew to comparable overall sizes, and maintained a broad cell-type composition similar to control organoids. This indicated that *LINC00662* is not required for the initial specification of neuroectoderm or the basic division of early progenitor cells.
- **Neuronal Maturation and Outgrowth Phase (Day 30):** By day 30 of differentiation, when neural progenitors actively exit the cell cycle, migrate outward from the ventricular-like zones, and extend dense networks of axons and dendrites, a pronounced developmental divergence emerged. Immunohistochemical staining and quantitative imaging revealed that *LINC00662*-suppressed human organoids exhibited a statistically significant reduction in TUJ1 (neuron-specific class III beta-tubulin), a primary structural protein of the microtubule cytoskeleton that forms the physical backbone of developing axons and neurites. A second marker associated with maturing dendritic extensions, MAP2 (microtubule-associated protein 2), also exhibited a downward trend in the suppressed organoids.

When *LINC00662* was switched off in human brain organoids, newborn neurons struggled to mature properly and failed to extend their axonal and dendritic projections as prolifically as normal human neurons. Rather than causing catastrophic tissue

collapse—which would have been fatal to ancestral chimpanzees had the viral insertion occurred in an essential survival gene—the silencing of *LINC00662* subtly modulated the kinetics, structural robustness, and exuberance of neurite outgrowth during early cortical assembly.

Experimental Manipulation	Cellular Model System	Target Locus / Molecule	Molecular Technique	Primary Observed Phenotype
Baseline Comparative Profiling	Human vs. Chimpanzee iPSCs & Day 15 Neural Organoids	Genome-wide PTERV1 loci & <i>LINC00662</i>	Oxford Nanopore Long-Read Methylation & snRNA-seq	158 PTERV1 loci heavily methylated in chimp; <i>LINC00662</i> highly expressed in human but completely silent in chimp.
Viral Excision (Gain-of-Function Rescue)	Chimpanzee iPSCs	Intronic PTERV1 provirus inside <i>LINC00662</i>	CRISPR-Cas9 targeted deletion using flanking sgRNAs	Complete restoration of <i>LINC00662</i> transcription in chimpanzee stem cells, proving epigenetic silencing is driven by the virus.
Interactome Mapping	Human Neural Cells	<i>LINC00662</i> RNA transcript	Biotinylated RNA Pulldown + LC-MS/MS Proteomics	Specific binding of <i>LINC00662</i> to RNA-binding proteins regulating mRNA processing, cytoskeleton dynamics, and neurite growth.
Targeted Transcriptional Repression (Loss-of-Function)	Human iPSCs & Day 15 to Day 30 Neural Organoids	Human <i>LINC00662</i> Promoter	CRISPRi (dCas9-KRAB) with two independent sgRNAs	Normal organoid formation at Day 15, followed by significantly reduced TUJ1+ neuronal cytoskeleton staining and impaired neurite extension by Day 30.

7. Evolutionary Synthesis: How Retroviral Epigenetics Shapes Speciation

The discovery that an ancient PTERV1 insertion silenced *LINC00662* in chimpanzees offers a nuanced perspective on the genetic architecture of primate brain evolution. For decades, popular accounts of human origins have often framed the human brain as the product of a linear, cumulative march of genetic additions—a series of beneficial mutations that progressively upgraded an ancestral ape brain into a modern human mind. Yet evolutionary biology operates without foresight, working through opportunistic modifications in every diverging branch of a phylogenetic tree.

As Patricia Gerdes emphasized in discussing the team's findings, the silencing of *LINC00662* by PTERV1 does not by itself explain the threefold difference in brain volume or the cognitive gap between humans and chimpanzees. Brain evolution is profoundly polygenic, involving thousands of regulatory adjustments across millions of years. Rather, the *LINC00662*-PTERV1 mechanism illustrates a fundamental principle of evolutionary developmental biology (evo-devo): changes in the timing (heterochrony) and spatial dynamics of neuronal maturation are central drivers of brain divergence among primates.

In comparative neurobiology, one of the most well-documented differences between human and non-human primate neurodevelopment is the pace of neuronal maturation. Compared to macaques and chimpanzees, human cortical neurons undergo a remarkably protracted period of maturation—a phenomenon known as developmental neoteny. While this prolonged maturation phase keeps human neurons plastic for much longer into childhood, human neurons ultimately construct far larger, more complex dendritic arbors and establish substantially denser synaptic connectivity across cortical layers than chimpanzee neurons. The active expression of *LINC00662* in the human lineage—retained from the pre-PTERV1 hominoid ancestor—supports the robust cytoskeletal scaffolding and neurite extension required to build these expansive axonal and dendritic networks. Conversely, when the PTERV1 retrovirus integrated into the ancestral *Pan* genome roughly four million years ago, the resulting epigenetic silencing of *LINC00662* steered chimpanzee neuronal maturation along a subtly different cellular trajectory.

The Broader Landscape of Transposable Elements in the Brain

Beyond the specific case of LINC00662, the Lund University study establishes a broader mechanistic paradigm for how infectious retroviral waves can accelerate speciation. Throughout mammalian history, populations have periodically endured germline colonizations by exogenous retroviruses. When a host species survives such an outbreak—or when one population is spared due to restriction factors like TRIM5alpha while a sister population is heavily colonized—the resulting endogenous retroviruses instantly introduce dozens or hundreds of lineage-specific structural variants across the genome.

Historically, geneticists focused on how the activation of ERV sequences (co-opting viral LTRs as novel enhancers or promoters) could wire new gene regulatory networks. For example, human-specific endogenous retroviruses (such as HERV-H and HERV-K) and primate-specific SVA (SINE-VNTR-Alu) retrotransposons have been co-opted in the human genome to act as enhancers in pluripotent stem cells and developing neural tissues. The work of Gerdes, Jakobsson, and colleagues demonstrates that the *repression* of ERVs is an equally potent evolutionary force. Because the KRAB-ZFP/TRIM28/DNA-methylation defense machinery treats every new proviral insertion as a threat to be entombed in heterochromatin, the colonization of the chimpanzee genome by 158 copies of PTERV1 simultaneously seeded 158 novel heterochromatin islands across the chromosomes. Wherever those heterochromatin domains landed close enough to an existing host promoter or enhancer to trigger epigenetic spreading, they instantaneously down-regulated or silenced adjacent host genes in a lineage-specific manner.

This dual capacity of endogenous retroviruses—capable of acting as transcriptional activators when unmethylated, or as epigenetic silencers when targeted by host methylation—makes them uniquely powerful engines of regulatory divergence. Because these insertions occur rapidly during infectious waves rather than through the slow, steady tick of single-nucleotide point mutations, retroviral colonization events can punctuate evolutionary equilibrium, introducing rapid shifts in gene regulatory networks between diverging populations.

8. Methodological Limitations and Future Research Directions

While the Gerdes et al. (2026) study provides a rigorous mechanistic link between paleovirology, epigenetics, and neurodevelopment, several important limitations define the boundaries of the current findings and point toward future avenues of inquiry:

- **In Vitro Organoid Constraints:** Three-dimensional unguided neural organoids are transformative tools for modeling the first few weeks of embryonic forebrain development, capturing early neural progenitor proliferation, rosette organization, and initial neurite outgrowth. However, organoids lack vascularization, microglia (the brain's resident immune cells), sensory inputs, and the complex long-range anatomical circuitry of an intact, mature brain. Consequently, while CRISPRi suppression of *LINC00662* clearly reduces TUJ1-positive neurite scaffolding at day 30 in culture, exactly how this cellular phenotype translates to mature synaptic physiology, circuit firing patterns, or macroscopic cortical architecture in vivo remains to be determined.
- **Resolving the Exact Biochemical Mechanism of *LINC00662*:** Although the LC-MS/MS proteomics experiments successfully identified a network of neurite-associated RNA-binding proteins that physically interact with *LINC00662*, the precise stoichiometric and biophysical mechanics of these interactions require deeper dissection. Future structural biology and cross-linking immunoprecipitation (CLIP-seq) studies will be needed to determine whether *LINC00662* acts primarily by localizing these proteins to specific subcellular compartments (such as the growth cones of extending axons), stabilizing target mRNAs against degradation, or modulating alternative splicing of cytoskeletal transcripts.
- **The Remaining 157 PTERV1 Loci:** The chromosome 19 insertion inside *LINC00662* represents just one of the 158 methylated PTERV1 proviruses mapped in the chimpanzee genome. While many of the remaining 157 copies sit in deep intergenic deserts far from coding exons, human and chimpanzee genomes are organized into complex three-dimensional topologically associating domains (TADs) where distal enhancers loop over hundreds of kilobases to contact target promoters. Investigating whether the other 157 chimpanzee-specific heterochromatin domains disrupt distal enhancer elements, insulator boundaries (such as CTCF binding sites), or chromatin looping in other tissues—such as the

immune system, metabolic organs, or reproductive tract—represents a fertile frontier for comparative primate genomics.

9. Conclusion

The evolutionary story of *LINC00662* and PTERV1 serves as a striking reminder that the genome is not an isolated, self-contained digital script, but a living historical archive shaped by millions of years of ecological interactions with infectious pathogens. Roughly four million years ago, an ancient retrovirus swept through African primates. Equipped with an effective intracellular shield in the form of the human TRIM5alpha restriction factor, our hominin ancestors repelled the virus, preserving the ancestral open chromatin state at the *LINC00662* locus on chromosome 19 and retaining a long non-coding RNA that actively fosters the maturation and structural outgrowth of developing human neurons. Chimpanzees, by contrast, absorbed the virus into their germline, and the epigenetic armor deployed by their cells to silence the invader permanently switched off its neighboring neurodevelopmental gene. Through the convergence of paleovirology, long-read nanopore epigenomics, CRISPR genome engineering, and stem-cell organoid modeling, modern biology is finally beginning to read between the lines of our shared coding DNA—revealing how the silent viral ghosts of prehistoric pandemics helped sculpt the divergent minds of primates.