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The war within our DNA



© **FRANK JACOBS**, Assistant Professor in the Molecular Neuroscience group, Swammerdam Institute for Life Sciences (SILS) of the UvA.

→ Throughout evolution, the human DNA has been invaded by multiple classes of ancient retroviruses. These viruses have become extinct long ago, but their DNA traces still linger in our genome, where they have given rise to what we now call retrotransposons. These virus-like genetic elements have maintained the ability to multiply and insert new copies of themselves into our DNA. New retrotransposon insertions can disrupt genes and cause disease, which forces us —the host genome— to come up with mechanisms to prevent these molecular jumping events.

Genetic cat-and-mouse games
Retrotransposons are responsible for the vast majority of non-coding DNA in our genome, often referred to as junk DNA. Throughout primate evolution, retrotransposons have frequently changed their basic composition, a phenomenon reminiscent of the evolution of viruses to evade detection by the host. Because the majority of retrotransposons seem to be efficiently repressed, we know that a defence mechanism must

exist in the host genome that restricts the invasion of each newly modified retrotransposon type. The mechanism that ‘chases’ the retrotransposons has remained elusive for a long time. Pioneering work in the labs of Stephen Goff and James Thomas suggested that so-called KRAB zinc finger (ZNF) genes — encoding a large family of transcriptional repressor proteins — are involved in the genome’s defence against retrotransposon invasions. The human genome harbours more than 400 KRAB ZNF genes. Almost half of these — 170, to be exact — exist only in primates. Therefore, we and others hypothesised that the unusual expansion of KRAB ZNF genes in primates is the result of evolutionary pressure on these species to deal with new, primate-specific retrotransposon invasions.

In our study, we took on the challenge to identify the genes that have evolved to repress two classes of primate-specific retrotransposons that have been active throughout the so-called great ape evolution. After multiple years of searching, using different genetic approaches, we identified two primate-specific KRAB ZNF genes, ZNF91 and ZNF93, which evolved to repress these retrotransposons. In both cases the ancestral versions of these KRAB ZNF genes had already emerged in our genome just before the invasion of the retrotransposon started. By looking at the composition of these genes in other primates we found that soon after the invasion of the new retrotransposons began, the dedicated KRAB ZNF gene rapidly evolved to specifically recognize and repress these new retrotransposons. This success did not mean, however, that the battle was won. Although repression initially severely restricted the retrotransposon in its actions, it was not completely defeated and we found evidence that one of the retrotransposons eventually managed to escape repression of ZNF93 by simply shedding the

ZNF93 binding site a few million years further down the evolutionary road. This event gave rise to a new retrotransposon element that is still actively copying and pasting itself in our genome today.

The specific example described above is just a snapshot of a never-ending race (Figure 1). KRAB ZNF genes have been rapidly expanding and evolving in primate genomes, precisely because the retrotransposons are continuously evolving to escape their repression. When retrotransposons manage to do so, the host cannot allow the KRAB ZNF gene in charge of repressing the old element to co-evolve with this change, as it would release the repression of the old elements. Furthermore, the different KRAB ZNF genes also obtain other functions and become essential for normal cellular functioning. So, instead, a newly duplicated KRAB ZNF gene needs to step up to the challenge and rapidly evolve to become the repressor of the newly emerged retrotransposon subtype, driving the genome and gene regulatory networks to a progressively more complex state.

Brainy retrotransposons escape repression

For unknown reasons, retrotransposons are less efficiently silenced in brain cells than in other cell types. This suggests that recent retrotransposon insertions could

→ References

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affect gene expression in the human brain, raising all sorts of new, intriguing questions. How well is the gene-regulatory effect of retrotransposons kept under control during development and aging of the human brain? Could dysregulation of mobile genetic elements be a contributing factor to complex human neurological disorders? These are the big questions that are central to the research done in our lab at the University of Amsterdam right now. Using embryonic stem cell-derived cortical tissues from human and monkey origin, our lab currently investigates how retrotransposon invasions have reshaped the gene regulatory networks involved in human brain development. Our research explores the possibility that evolutionary novelties such as retrotransposon insertions may directly relate to humans’ increased susceptibility to neurodevelopmental disorders such as autism and schizophrenia and disorders associated with the aging brain such as Parkinson’s and Alzheimer’s. If successful, these studies will have a big impact on our thinking about complex human brain disorders. Ω

