The war within our DNA

Jacobs, F.

Published in:
Amsterdam Science

Citation for published version (APA):
The war within our DNA

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 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 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 insertions 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.

→ References