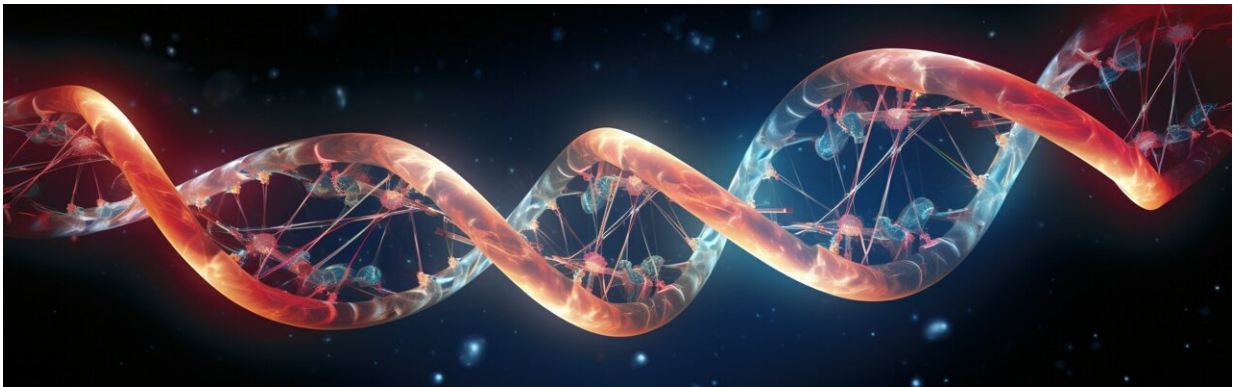


Transposons: From 'selfish' genes to key elements in biological processes

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Double Helix generated by AI. Credit: Remo Sanges

In 2001 the sequencing of the human genome revealed a surprising fact: over 45% of our genome comes from sequences called transposons, "jumping" genes that can move within the genome, generating new copies of themselves through molecular mechanisms of cut-and-paste or copy-and-paste.

Because of this characteristic, they are also called "selfish genes," interested only in replicating, in a way similar to the action of viruses. However, new research carried out in collaboration between SISSA—Scuola Internazionale Superiore di Studi Avanzati and IIT—Istituto Italiano di Tecnologia, led by Professors Stefano

Gustincich and Remo Sanges, has revealed important and unexpected functions associated with these transposons, debunking their reputation as selfish genes.

Selfish jumpers

Most of the copies generated by transposons are inactive today, but in the [human genome](#) and that of other mammals there are about a hundred copies of transposons belonging to the so-called LINE (Long Interspersed Nuclear Elements) family that are still potentially active. This means they can be transcribed, producing messenger RNAs that, when translated into proteins, can also contribute to a copy and paste process of genetic sequences.

This ability of LINE transposons poses a potential risk to genome integrity: the random insertion of a new gene copy could interfere with important genetic functions. To protect against this danger, over the course of evolution, organisms have developed cellular defense mechanisms capable of blocking or limiting the activity of transposons, thus helping to preserve genome stability.

The research

The fundamental question of why our genome allows and finely regulates the activity of transposons was the [driving force](#) behind the research conducted by the laboratories of Professors Sanges and Gustincich. The studies carried out by the two research centers led to the publication of three articles with unexpected results that shed new light on the potential contribution of LINE elements to molecular processes in living organisms.

The first article, "LINE-1 regulates [cortical development](#) by acting as

long non-coding RNAs," published in *Nature Communications*, shows that the RNA produced by LINE transposons is essential for the development of the cerebral cortex in mice. Without this RNA, the cerebral cortex does not develop correctly, and the proportion of the different cell types that make up this organ is compromised.

According to the study's lead author, IIT researcher Damiano Mangoni, "One of the most important messages emerging from this work is that there are thousands of potential non-coding RNAs produced by LINEs that have gone unnoticed until now and play an active role in molecular processes, enabling the proper development and functioning of the brain."

The second article, "In silico characterization of minor wave genes and LINE-1s transcriptional dynamics at murine zygotic genome activation," published in *Frontiers in Cell and Developmental Biology*, examines data related to the early stages of embryonic development when a two-cell embryo begins to produce its own RNA.

The key discovery is that LINE elements are recognized by protein complexes that initiate transcription processes essential for proper embryonic development.

Federico Ansaloni, the study's lead author and former SISSA Ph.D. student, now a researcher at the Karolinska Institute in Stockholm, remarks, "Studying the very early stages of embryonic development allows us to outline the biological processes underlying the formation of a new individual. I find it fascinating that transposons, long considered junk DNA, are actually key elements in such a delicate process."

Finally, the article "Exploratory analysis of L1 retrotransposons expression in autism," published in *Molecular Autism*, examines how LINE transposons behave in the brains of people with autism spectrum

disorders. What the researchers discovered is that the transcription regulation of these sequences is different only in a small group of individuals with autism.

The data analysis also identified a group of genes containing LINE copies that, when activated, suppress the transcription of the host genes, suggesting that these sequences contain specific signals recognized by cell regulatory mechanisms.

According to Giovanni Spirito, the study's lead author, former SISSA Ph.D. student, and now a researcher at the Centre for Personalized, Preventive, and Predictive Medicine in Valle d'Aosta (CMP3VdA), "Our work suggests that, in some cases, autism may be caused by a mutation in a gene that controls the LINES. For these cases, the development of drugs capable of restoring control of these elements could be helpful in treatment."

Future perspectives

Remo Sanges, coordinator of the Ph.D. in Functional and Structural Genomics at SISSA and co-coordinator of the research, states, "It is fascinating to observe that, once the ability to identify transposon sequences evolved, our genome developed the ability to exploit these selfish elements to its advantage, using them as signals that can turn on or off entire transcriptional programs, making them indispensable for normal embryonic and brain development."

Stefano Gustincich, co-coordinator of the research, former SISSA professor, and current director of the RNA Central Laboratory at IIT, adds, "The community began to observe that these elements were functional and important in the brain, but most of the attention until now has been focused on the impact of generating new copies."

"With our research, it turns out that the most important functionality of these elements is at the RNA level and therefore independent of creating new copies. This discovery could explain why many copies of these elements are kept active and finely regulated in the [genome](#) of all living beings."

These studies, as agreed upon by the authors, pave the way for new and innovative lines of research aimed at identifying and understanding the regulatory signals present in [transposon](#) sequences and their primary functions, as well as identifying new treatments for neurodevelopmental and aging-related disorders.

More information: Damiano Mangoni et al, LINE-1 regulates cortical development by acting as long non-coding RNAs, *Nature Communications* (2023). [DOI: 10.1038/s41467-023-40743-7](https://doi.org/10.1038/s41467-023-40743-7)

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