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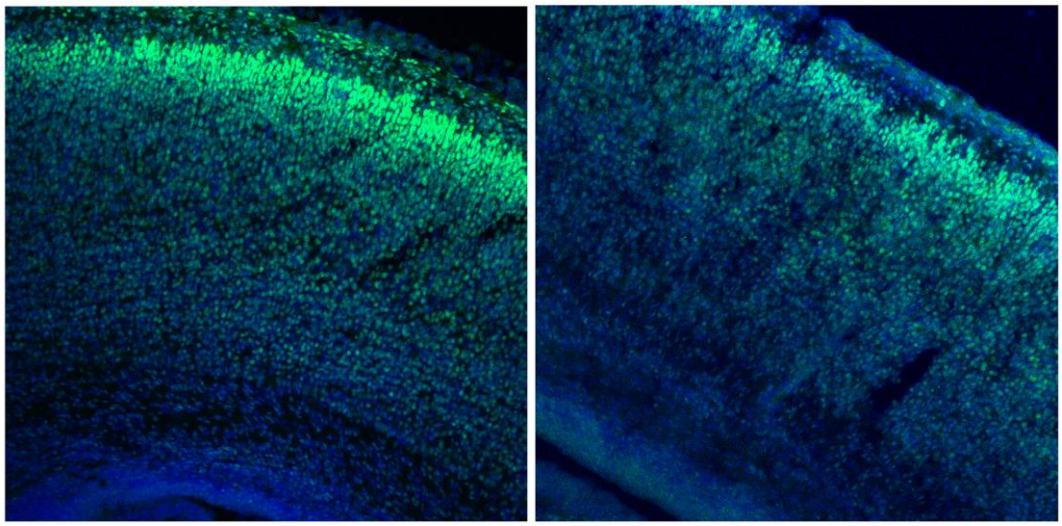
PRESS RELEASE

An orchestra conductor for “jumping genes”

A new study by SISSA, recently published in Development, shows that Foxg1, the “master gene” of key processes taking place in the developing brain, also finely regulates the biology of certain retrotransposons, or “jumping genes”.



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FOXG1 is a fundamental gene for brain development, and in particular for the formation and organisation of the cerebral cortex, the site of complex functions such as sensory perception and conscious thought. Mutations in this gene can cause FOXG1 syndrome, a rare genetic disorder characterised by severe behavioural and cognitive symptoms, along with structural brain abnormalities. FOXG1 is what is known as a “master gene” of neurodevelopment: it is a transcription factor that acts like an orchestra conductor, coordinating and deactivating hundreds of other genes necessary for brain development.

New research published in the scientific magazine Development, by Gabriele Liuzzi and Antonello Mallamaci of the SISSA Laboratory of Cerebral Cortex Development in Trieste, shows that this regulatory role of FOXG1 also extends to certain families of “jumping genes”, finely modulating their biology.

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Specifically, these are LINE1 retrotransposons, which can “copy and paste” themselves into new regions of the genome through an RNA intermediate. As such, retrotransposons were initially considered “selfish” genetic elements, interested only in replicating themselves, akin to viruses. Today, however, we know that they contribute to the regulation of other genes, are essential for the proper unfolding of neural development, and likely contribute to increasing genetic diversity in brain cells. We also know that excessive activation of retrotransposons can cause harmful mutations and compromise cell function. For this reason, retrotransposons are subject to particularly stringent and careful control.

“The surprise in this case is that Foxg1 behaves bimodally, i.e. as both repressor and activator: in neuronal progenitors and neurons, it reduces retrotransposon transcription, but - paradoxically - it also promotes amplification of their DNA, in certain regions of the mouse brain and during specific phases of its development” explains Gabriele Liuzzi, lead author of the research. “Specifically, FOXG1 physically binds to the mRNA of LINE1 retrotransposons, facilitating reverse transcription, i.e. the RNA-templated synthesis of new DNA retrotransposon copies”.

“As far as we know, FOXG1 is the first gene involved in the development of the nervous system that acts as a bimodal regulator of retrotransposons”, adds Antonello Mallamaci, director of the Laboratory of Cerebral Cortex Development. “This fine regulation of LINE1 retrotransposons by FOXG1 suggests a functional role. This follows the recent experimental demonstration of the essential role that retrotransposons play in brain development”.

The relationship between FOXG1 and retrotransposons could be key to gaining a better understanding of FOXG1 syndrome in humans. Too much or too little FOXG1 activity could alter key quantitative aspects of the biology of LINE1 elements, likely contributing to the symptom profile of patients. Knowledge of these dynamics could prove essential for developing new therapies in the future.

LINK UTILI
Paper:
Development

IMAGE:
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