Amyotrophic lateral sclerosis: The role of the circular RNA

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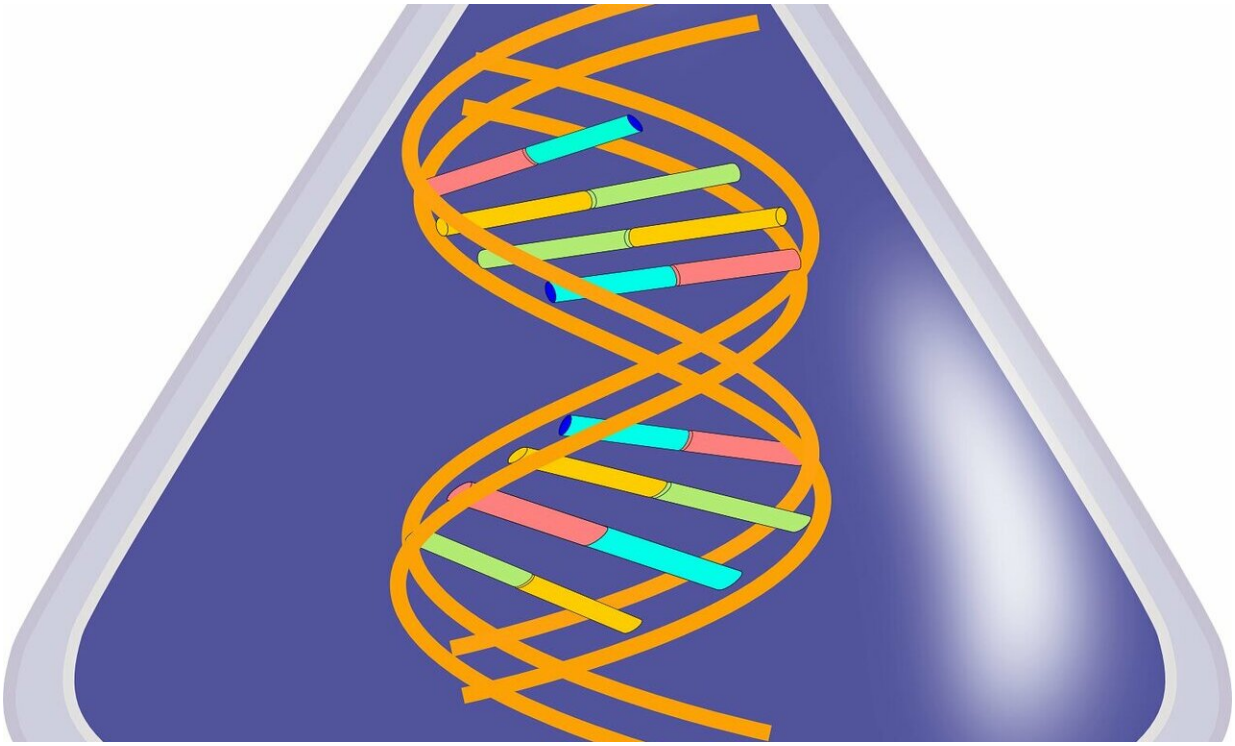

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A group of researchers from Sapienza University of Rome and the University of Perugia, in collaboration with the Italian Institute of Technology (IIT) has published a study which sheds light on a new form of RNA and its involvement in neurodegenerative disorders such as Amyotrophic lateral sclerosis.

Amyotrophic lateral sclerosis, known as ALS, is a neurodegenerative disorder which affects motor neurons. These are the neuronal cells responsible for muscle innervation, whose degenerations leads to progressive paralysis culminating with motor and respiratory failure. Two forms of ALS can be identified: the familial form which is due to specific genetic mutations, and the sporadic form whose pathogenesis is not related to clear congenital family history and whose causes are still mostly unknown. Although numerous studies have allowed the characterization of various proteins involved in ALS, there is still much to discover regarding the complexity of the onset and progression of the disease, and above all, on its possible treatment.

The research team belonging to Sapienza University of Rome's Charles Darwin Department of Biology and biotechnology and the Centre for Life Nano- & Neuro-Science of the Italian Institute of Technology (IIT) of Rome coordinated by Irene Bozzoni, and in collaboration with Mariangela Morlando of the University of Perugia, has added a new step towards the understanding of this pathology, identifying the circular RNA circ-Hdgfrp3 as a new molecular component of the pathological aggregates that are characteristic of ALS.

This type of RNA has been named as circular due to their peculiar shape, which endows them with a particular resistance to degradation. They represent a new class of molecules expressed in all cells, particularly in the nervous system, where their malfunctioning has been associated with different pathological states.

The study published in the journal *iScience* analyzes the presence of this specific circular RNA in association with ALS: more precisely, it has been identified within the pathological aggregates produced by mutations of the FUS protein that are associated with a severe form of the disease. Indeed, the FUS protein which normally localizes in the nucleus, is found in the cytoplasm as a result of specific mutations. Here,

it can aggregate forming large inclusions typical of ALS, which sequester many cellular components, preventing their correct localization and function.

The research group studied the effects of mutations in the FUS protein on the localization of this circular RNA using advanced imaging techniques and studying motor neurons of animal models reproduced in vitro. While in healthy motor neurons the circular RNA moves along the extensions of neurons, thus suggesting an important shuttle function to and from the periphery of the cell, in pathological conditions it remains trapped in FUS aggregates. This indicates that the formation of such pathological agglomerates can have a deleterious effect on the normal shuttling functions of this circular RNA and thus contribute to the malfunctioning of motor neurons.

"In this study we have defined the features of this circular RNA—says Irene Bozzoni, head of the Sapienza group—and described the alterations of its intracellular localization that occur in motor neurons bearing mutations for the FUS protein that are associated to ALS".

This research, financed by the European Research Council (ERC) and the AriSLA Foundation, opens new interesting frontiers for the understanding of neurodegenerative disorders, concerning the role of pathological aggregates and the RNAs contained within them.

More information: Eleonora D'Ambra et al, Circ-Hdgfrp3 shuttles along neurites and is trapped in aggregates formed by ALS-associated mutant FUS, *iScience* (2021). DOI: 10.1016/j.isci.2021.103504

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