Discovery of a potential therapeutic target for ALS

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University of Malta researchers have discovered a potential new drug target for amyotrophic lateral sclerosis (ALS), according to a new study published in the *Neurobiology of Aging* journal.

ALS is a progressive neurological disease affecting the nerve cells, known as motor neurons, that control muscles of the body. Due to the

disease, muscles stop functioning leading to difficulties with walking, talking, eating, and, eventually breathing.

In the study, researchers switched off the gene SCFD1 in fruit flies to discover that this triggered ALS symptoms. Similar to patients, the organisms developed reduced mobility and a deterioration of the contact points between nerves and muscles. Flies are used in ALS research because of considerable genetic and biological similarities to humans.

"The SCFD1 gene is one of the strongest risk factors for ALS patients globally. However, the significance of the connection between SCFD1 and the disease has remained unknown," explained the study's lead researcher Prof. Ruben J. Cauchi, Ph.D., associate professor of neurogenetics at the University of Malta.

SCFD1 popped up on the radar of ALS genetics in a recent monumental study by Project MinE that scrutinized the genes of hundreds of thousands of ALS patients and healthy volunteers worldwide.

"These gigantic studies have the power to discover genes that are commonly altered in ALS patients compared to those without the disease. However, their unbiased approach means that they often churn out genes whose link to ALS remains ambiguous," said Prof. Cauchi.

When scouting for molecular defects in cells in which SCFD1 was switched off, the researchers found that the cell's ability to fold proteins is compromised. Proteins need to be correctly folded into complex 3D structures to perform their vital functions.

It is well known that motor neurons already have a suboptimal ability to fold proteins correctly and factors that dampened this further are predicted to increase susceptibility to ALS. This includes alternations that damage the SCFD1 gene. Repairing or activating SCFD1 in patients

is thus expected to slow or stop their disease.

The research team know that they are on the right track because, in a historic decision, a drug that targets protein misfolding (AMX0035, marketed as Relyvrio) has been approved by the U.S. Food and Drug Administration (FDA), last year.

More information: Rebecca Borg et al, Loss of amyotrophic lateral sclerosis risk factor SCFD1 causes motor dysfunction in Drosophila, *Neurobiology of Aging* (2023). DOI: 10.1016/j.neurobiolaging.2023.02.005

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