MedicalXpress

New insight into the most common genetic cause of ALS and FTD

June 30 2016

Scientists from the University of Sheffield have discovered a novel function of the C9orf72 protein which is linked to amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) - giving a new insight into the most common genetic cause of the degenerative diseases.

The pioneering study, conducted by researchers from the world-leading Sheffield Institute of Translational Neuroscience (SITraN), found that the C9orf72 protein, which is encoded by the C9ORF72 gene, functions in the autophagy pathway - something which is defective in patients with the most common inherited form of ALS and FTD.

Mutations in the C9ORF72 gene carry a well-established risk for ALS, also known as motor neurone disease (MND), and FTD which is the second most common cause of dementia in people under 65. However, until now the basis for this link has been unclear.

Scientists believe one of the ways the C9ORF72 mutation may cause ALS and FTD is by reducing the amount of C9orf72 protein present in the cells - something which is very hard to verify without a clear understanding of the function of the C9orf72 protein.

The Sheffield team led by Dr Kurt De Vos and Dr Andy Grierson investigated the role of the C9orf72 protein in nerve cells and found it regulates the initiation of a vital process called 'autophagy', which helps the cell to dispose of damaged proteins and cell parts, and recycles cell nutrients.

Dr De Vos said: "Our study provides compelling evidence that the C9orf72 protein is required for the initiation of autophagy, a pathway essential for the survival of nerve cells.

"We could also show that that loss of C9orf72 protein function mimics the specific pathology observed in our ALS and FTD patients."

Dr Andy Grierson, fellow lead investigator, added: "Diseases such as ALS and FTD are commonly associated with large protein clumps that accumulate in affected nerve cells. Our data now shows that the C9orf72 protein is involved in the cellular pathway that should dispose of these clumps and that the autophagy process is defective in the cells of our ALS and FTD patients.

"Further studies are needed to confirm if defective autophagy contributes to the disease process, but if this bears out then autophagy drugs may be beneficial for patients."

The pioneering study, published in the *EMBO Journal* was supported by the Thierry Latran Foundation, Medical Research Council (MRC), MND Association, Alzheimer's Society, European Union and the University of Sheffield Moody Endowment Fund.

Dr Valerie de Broglie, Director of the Thierry Latran Foundation, said: "We are pleased to see the positive outcome of the research selected by our European Scientific Advisory Board. Better understandings of pathways involved in ALS are of upmost importance to move towards a therapy."

Dr Doug Brown, Director of Research at Alzheimer's Society, said: "Frontotemporal dementia is the second most common form of dementia in those under the age of 65, and can include some upsetting symptoms, yet we know relatively little about its underlying causes.

"This study reveals what happens in the brain cells of people with a gene mutation that is known to cause frontotemporal dementia. Identifying the effects of faulty genes is a vital first step to being able to design drugs that could best help people living with the condition. The gene, known as C9ORF72, was only linked to dementia in the last five years so it's encouraging that advances are being made to piece together the important role it plays in the brain."

Dr Sadie Vile, Research Grants Manager at the MND Association, added: "Although only about 10 per cent of MND cases are inherited, study of the genetic causes helps to understand the non-inherited or sporadic forms. The C9ORF72 gene was identified in 2011 as the most common cause (about 40 per cent) of all inherited MND.

"The autophagy process has been linked to other MND-causing genes, so it is interesting that evidence is now building up to connect this important cellular process to the C9orf72 protein. We are very proud that Emma Smith, one of our MND Association PhD students, has played a key role in this important piece of research."

More information: Christopher P Webster et al. The C9orf72 protein interacts with Rab1a and the ULK1 complex to regulate initiation of autophagy, *The EMBO Journal* (2016). DOI: 10.15252/embj.201694401

Provided by University of Sheffield