November 2020 MND Research Article summary – Sarah Roscoe, PhD student, University of Sheffield

Results from a large-scale analysis study linking weight loss to ALS genetics

Genome-wide Meta-analysis Finds the ACSL5-ZDHHC6 Locus is Associated with ALS and Links Weight Loss to the Disease Genetics (Iacoangeli et al., October 2020, Cell Reports, Vol 33, Issue 4., DOI: https://doi.org/10.1016/j.celrep.2020.108323)

Accounting for 65-85 % of MND cases, amyotrophic lateral sclerosis (ALS) is an incurable, progressive neurodegenerative disorder. Although frequently overlooked, people living with ALS (plwALS) often experience problems with their nutrition, with approximately 16 – 53 % of plwMND becoming malnourished and experiencing significant weight loss during the course of the disease. Weight loss is known to be a factor responsible for speeding up the progression of MND, and shortening life expectancy. It is therefore important to monitor and understand changes in the nutritional status of plwALS. Currently, this is done by measuring people’s weight and body composition; which can be broken down into the proportion of body fat and ‘non-fat’ mass (i.e., everything else in the body, including bones, organs and muscles).

Genes are instruction manuals for the cell, made from sections of DNA; genes tell the cell what to do. Variations from the correct sequence of DNA within a gene are called mutations. The entire set of an organism’s instructions is known as a genome. These instructions have been identified and named in genetic databases.

ACSL5 is a gene known to play a key role in the conversion of nutrients from food and fluid intake into fatty acids (the building blocks of fat in the body). Mutations in the ACSL5 gene have previously been linked to rapid weight loss. The authors of this report conducted a large-scale analysis of three independent ALS genetic databases, comparing the entire genomes of 86,196 individuals (22,877 plwALS and 63,319 healthy controls) across multiple ethnicities (Chinese, European and Australian). They noticed a change in the DNA sequence of ACSL5 in plwALS, but not in the healthy controls.

They then investigated the effect of this change within the ACSL5 gene with body composition, body mass index and weight in 77 plwALS and 77 healthy controls. For 67/77 plwALS, they were able to compare weight and body composition measurements taken during the course of the disease, with the presence of the ACSL5 mutation. They noticed that patients with the ACSL5 mutation had a much lower muscle mass than healthy individuals, which declined more rapidly, over a shorter period of time. This means that the development of ALS is sped up for these individuals, resulting in a shorter life expectancy.

Whilst this report highlights the involvement of ACSL5 in weight loss in ALS patients, these results are unable to distinguish whether ACSL5 causes weight loss as a result of ALS, or whether ALS is a result of weight loss, due to variations within ACSL5. A larger sample size, with measurements collected over a longer period of time are needed to make more certain conclusions between ACSL5 and its involvement in weight loss in ALS.