Research progress in Ullrich congenital muscular dystrophy

Ullrich congenital muscular dystrophy (UCMD) is a muscle wasting condition that is either present at birth or is noticed in children during their first months of life. The first symptoms are muscle weakness and hypotonia (something also described as floppy baby syndrome). The muscle weakness is often very severe and many children will never be able to stand, walk or run, or they will lose this ability in their first decade of life. Breathing is also one of the main problems that worsen during their teenage years and the young adults will need the help of a ventilator to survive.

UCMD is a very rare condition that occurs in only one in a million people and there are less than 100 individuals known in the UK to have this condition. It is a genetic condition that can be passed down from the parents but can also spontaneously appear without a previous family history.

The genetic cause of UCMD

The condition develops as a result of mutations in the genes that make the collagen VI protein complex. Production of three proteins from three genes called COL6A1, COL6A2 and COL6A3 is necessary to form the collagen VI protein complex. Several of these complexes come together to form a mesh-like structure. Mutations in each of those genes have been found to cause UCMD and to date more than 200 different mutations have been identified.

Mutations in the collagen VI genes are also associated with a disruption in the function of mitochondria which are the batteries of the cells and provide them with energy. Muscle cells of individuals with UCMD have lost the ability to dispose of and recycle damaged mitochondria which in turn leads to an increased death of muscle cells. This is thought to be a major contribution to muscle wasting.

The genetics of UCMD is complicated; it can be inherited in a dominant (one faulty copy of the gene is sufficient to cause the condition) or recessive (two faulty copies of the gene are necessary to cause the condition) way.

Our understanding of UCMD is constantly improving. The collagen genes carrying the primary genetic defect for the recessive and dominant form of UCMD have been identified and thoroughly studied. However, questions still remain on how the absence of collagen VI actually leads to the symptoms seen in UCMD and more research is needed to clarify this.

The use of mouse models has already proved invaluable in understanding UCMD in more detail and assessing the benefits of potential therapeutics. These current models, however, may not reflect the true severity of the condition in humans and more work is needed to develop more useful models.

Clinical approaches to treat UCMD

Therapeutic approaches to address the underlying primary genetic defects in UCMD are in their infancy. For patients with dominant UCMD, these approaches focus on
rendering the mutated gene copy inactive to allow the production of functional collagen VI. For the recessive form of the condition the aim is to deliver a functional collagen gene to the muscle cells of patients.

Work on clinical trials is progressing. The first set of clinical outcome measures have been defined, but scientists are now looking for biomarkers to better monitor the progression of the condition and assess the benefit of potential drugs and treatments in clinical studies more accurately. Preclinical studies in mouse models have identified some possible therapies that address the symptoms of UCMD but there is the question of whether the benefit of these potential treatments can be reproduced in clinical trials in humans. Furthermore, additional work is needed to look at therapeutic avenues that address the underlying genetic cause rather than just the symptoms of the condition.

The impact of MDUK on UCMD research

In the last ten years the charity supported three research projects in the group of Professor Kate Bushby at Newcastle University and the results were crucial to better understanding the role of collagen VI mutations as a cause of UCMD, to developing diagnostic tests and to providing first evidence for the usefulness of cyclosporine A as a treatment.

Provisions have been made for the National Neuromuscular Database which is a natural history database for the collection of clinical data from patients with UCMD. These data have been crucial to understanding the progression of the condition in more detail and provided the basis for the work of the clinical fellow in Professor Francesco Muntoni’s laboratory to develop tests that measure the benefits of potential treatments in clinical trials.

An award was made for a project aimed at developing a gene therapy approach for people with the dominant form of UCMD. Professor Francesco Muntoni and his group are developing an adaption of the exon-skipping technology to selectively silence the mutated gene copy and leave the healthy gene-copy untouched to produce a functional collagen VI protein complex.

The charity funded a clinical trial co-ordinator in the group of Professor Francesco Muntoni at the Institute of Child Health in London. One aspect of the role was to provide crucial administrative support for finalising the clinical trial protocol for the omigapil clinical study (CALLISTO) which is the only ongoing clinical trial for UCMD. It is a phase I study to evaluate the safety and efficacy of omigapil in children and adolescents with UMCD. It is currently recruiting participants in the USA.