

Secondary pathogenetic mechanisms in X-linked myotubular myopathy and centronuclear myopathies (CNM)

Myotubular and centronuclear myopathy (CNM) are inherited muscle conditions associated with severe weakness and characteristic changes on muscle biopsy. X-linked myotubular myopathy (XLMTM) is the most severe form and affects almost always boys, whereas those forms due to changes in the dynamin 2 (*DNM2*), amphiphysin 1 (*BIN1*) and skeletal muscle ryanodine receptor (*RYR1*) gene do not have any sex preference. In addition to skeletal muscle, other organs such as the liver ("hepatic peliosis") or the lens of the eye may be affected in XLMTM and *DNM2*-related CNM, respectively.

Understanding the causes of muscle weakness and wasting in XLMTM and CNM is important for the development of effective therapies for these conditions. Although the genetic defects underlying the centronuclear myopathies are now largely known, the precise mechanisms by which those faults cause severe weakness and associated complications are currently not fully understood.

However, recent research findings suggest two promising new lines of further investigation:

- Firstly, there is emerging evidence that faults in the *RYR1* and *MTM1* gene may be associated with impairment of muscle contraction due to primary or secondary defects of calcium release. Muscle contraction is the endpoint of an intricate process. (This is often referred to as "excitation-contraction coupling") This process is triggered by a nerve impulse sent from the brain and subsequently prompts calcium release into muscle cells. Faults may occur at any stage of this process and have been associated with other neuromuscular conditions.
- Secondly, recent research work suggests that CNM associated with faults in the *DNM2* gene (and probably other CNM-related genes) are associated with defects in the autophagy pathway, an important housekeeping system in muscle and other cells too. Autophagy (Greek for "self-digestion") is a "recycling" mechanism that helps all cells (including muscle cells) to get rid of the waste and to reallocate vital resources within the cell. Defects in this pathway have been associated with other neuromuscular conditions and may explain some of the non-muscular complications in XLMTM and CNM patients.

In the present project we will investigate different aspects of calcium release, excitation-contraction coupling and the autophagy pathway in patients affected by XLMTM and other forms of CNM. This work will provide further insight into the mechanisms causing weakness in CNM, and may provide the basis for the development of effective therapies to help and improve the quality of life of affected patients.

This project will be a joint effort between different research groups based in the UK and Switzerland that have successfully collaborated during the past decade. The different groups have strong scientific backgrounds and complementary expertise in different aspects of neuromuscular disorders. Dr Heinz Jungbluth (King's College, London, UK) has a longstanding interest in clinical and pathological aspects of the centronuclear myopathies and has led characterization of the form of CNM linked to faults in the *RYR1* gene. Jointly with Prof. Mathias Gautel and his team (also King's College, London) he has recently identified the genetic fault underlying Vici

syndrome, a rare multisystem disorder due to defective autophagy with muscle biopsy findings closely resembling CNM. Prof Mathias Gautel is a leading expert in the molecular biology of muscle cells, with a particular interest in muscle contractility and the role of the autophagy pathway in normal muscle development and functioning. Dr Susan Treves and Dr Francesco Zorzato head the Muscle Research group in the Department of Anesthesia and Biomedicine, Basel University Hospital, Basel, Switzerland. They have been interested in finding the mechanisms underlying muscle diseases and specifically how faults in genes involved in the regulation of calcium, lead to changes in the function of muscle.

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Dr Treves & Dr Jungbluth - October 2012

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