

## **Structural Studies of the inner DysF domain of Human Myoferlin**

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Abstract:

Muscular dystrophies are a group of inherited muscle diseases that cause muscle weakness and wasting. Mutations in the dysferlin gene, encoding the dysferlin protein, causes disruption to the muscle membrane repair mechanism and leads to two types of muscular dystrophies, limb-girdle muscular dystrophy type 2B (LGMD2B) and Miyoshi Myopathy. Dysferlin is part of a family of proteins known as the ferlins. Myoferlin, another ferlin family member, is required for skeletal muscle generation and is highly expressed during stages of muscle generation. This family of proteins consist of large proteins of over 2000 amino acid residues with multiple C2 domains and a C-terminal transmembrane helix. In some of the members there is also a domain of unknown structure and function known as the DysF domain, an unusual feature of which is that there are two copies, one 'nested' inside another as a result of an internal duplication event. As a result, the domain is referred to as two parts – the N-terminus region, DysFN and the C-terminus region, DysFC. Several mutations that affect muscle re-generation occur within this small domain. The structure of the 123 residue inner DysF domain of human myoferlin, determined by multidimensional heteronuclear NMR studies, has a unique fold, and the conserved regions of the structure show extensive tryptophan/arginine stacking, which is vital for folding of this domain. Point mutations in these residues give rise to muscular dystrophies.