Investigating Disease Mechanism in Myofibrillar Myopathy through Genetic Modelling in Zebrafish

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ABSTRACT:

Neuromuscular diseases constitute the majority of genetic disorders that affect skeletal muscle function. Myofibrillar myopathy (MFM) is a form of neuromuscular disorder characterized by muscle weakness and limited mobility. MFM is clinically and genetically heterogeneous and can have disease onset in patients from childhood to late adulthood. Mutations in 17 known genes create symptoms associated with MFM. While the exact biological progression of MFM is not entirely clear, z-disc disorganization in affected muscles is a common disease pathology among the different forms of MFM—causing structural defects and thereby function deficits in skeletal muscle. MFM is usually progressive and can affect skeletal and cardiac muscles. There are currently no treatments for MFM, due to a lack of understanding of the disease on a molecular level. Clinical studies are increasingly reporting novel mutations in MFM causing genes; however, the mechanism of these variants on skeletal muscle structure and function is unclear. We propose to model common MFM variants in cell culture and *in vivo* zebrafish models to observe their effects on sarcomere function and development. This approach allows for greater understanding of the *in vivo* impact of MFM causing mutations, as zebrafish exhibit a high genomic conservation and similar muscle composition to humans. An understanding of the disease mechanism is critical for the development of specific treatments. Thus, clarification of the mechanisms of MFM variants on mutant protein function in skeletal muscles will help establish suitable therapies for pre-clinical evaluation.

KEY TERMS:

Muscular Dystrophy- a genetic condition that causes progressive weakness of the muscles
Myofibrillar Myopathy- a genetic condition that weakens patients' skeletal muscles
Z-Discs- lines that define the edges of sarcomeres; anchor down the actin filaments
Myofibrillar disorganization- structural changes in the myofibrils, leading to reduced force generation in affected muscles.

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