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The Two Mutations of Actin-Myosin Interface and Their Effect on the Dynamics, Structures, and Functions of Skeletal Muscle Actin.

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Abstract

Congenital myopathy is a broad category of muscular diseases with symptoms appearing at the time of birth. One type of congenital myopathy is Congenital Fiber Type Disproportion (CFTD), a severely debilitating disease. The G48D and G48C **mutations** in the D-loop and the actin-myosin interface are the two causes of CFTD. These **mutations** have been shown to significantly affect the structure and function of muscle fibers. To the author's knowledge, the effects of these **mutations** have not yet been studied. In this work, the power stroke structure of the head domain of myosin and the wild and mutated types of actin were modeled. Then, a MD simulation was run for the modeled structures to study the effects of these **mutations** on the structure, function, and molecular dynamics of actin. The wild and mutated actins docked with myosin showed differences in hydrogen bonding patterns, free binding energies, and hydrogen bond occupation frequencies. The G48D and G48C **mutations** significantly impacted the conformation of D-loops because of their larger size compared to Glycine and their ability to interfere with the polarity or hydrophobicity of this neutralized and hydrophobic loop. Therefore, the mutated loops were unable to fit properly into the hydrophobic groove of the adjacent G-actin. The abnormal structure of D-loops seem to result in the abnormal assembly of F-actins, giving rise to the symptoms of CFTD. It was also noted that G48C and G48D did not form hydrogen bonds with myosin in the residue 48 location. Nevertheless, in this case, muscles are unable to contract properly due to muscle atrophy.

KEYWORDS: CFTD; H-bond formation analysis; MD simulation; actin-myosin interface; modeling

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