Modeling Cardiac Troponin: Molecular effects of calcium-activation of the thin filament and familial hypertrophic cardiomyopathy-related mutations

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The cardiac thin filament regulates actomyosin interactions, the key element of muscular contraction, through calcium-dependent alterations in the dynamics of cardiac troponin (cTn) and tropomyosin (Tm). Over the past several decades many details have been discovered regarding the structure and function of the cardiac thin filament and its components. We propose a dynamic, complete model of the thin filament that encompasses known structures of cTn, Tm and actin. By performing molecular dynamics simulations in two conditions, with and without calcium bound to site II of cardiac troponin C (cTnC), we found a combination of calcium-dependent changes in secondary structure and dynamics throughout the cTn-Tm complex. Our model demonstrates a comprehensive mechanism for calcium-activation of the cardiac thin filament consistent with previous, independent experimental findings. We then applied this model to investigate familial hypertrophic cardiomyopathy (FHC), a disease of the sarcomere that is the most common genetic cause of heart disease. Approximately 15% of FHC-related mutations are found in cardiac troponin T (cTnT), most of which are in or flanking the alpha-helical N-tail domain TNT1. TNT1 directly interacts with overlapping Tm coiled coils. Using our model we identified effects of TNT1 mutations that propagate to the cTn core where site II cTnC, the primary site of calcium binding and dissociation in the thin filament, is located. Specifically, we found that mutations in TNT1 alter the flexibility of TNT1 and that the flexibility of TNT1 is inversely proportional to the cooperativity of calcium activation of the thin filament. Further, we identified a pathway of propagation of structural and dynamic changes linking TNT1 to site II of cTnC. Mutation-induced changes at site II cTnC alter calcium coordination which corresponds to biophysical measurements of calcium sensitivity. Finally, we compared this pathway of mutational propagation with the pathway of the calcium activation of the thin filament and found that they are identical but opposite in direction.