Title:	Molecular mechanisms and structural features of cardiomyopathy-causing troponin T mutants in the tropomyosin overlap region
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Abstract:	Point mutations in genes encoding sarcomeric proteins are the leading cause of inherited primary cardiomyopathies. Among them are mutations in the TNNT2 gene that encodes cardiac troponin T (TnT). These mutations are clustered in the tropomyosin (Tm) binding region of TnT, TNT1 (residues 80-180). To understand the mechanistic changes caused by pathogenic mutations in the TNT1 region, six hypertrophic cardiomyopathy (HCM) and two dilated cardiomyopathy (DCM) mutants were studied by biochemical approaches. Binding assays in the absence and presence of actin revealed changes in the affinity of some, but not all, TnT mutants for Tm relative to WT TnT. HCM mutants were hypersensitive and DCM mutants were hyposensitive to Ca2+ in regulated actomyosin ATPase activities. To gain better insight into the disease mechanism, we modeled the structure of TNT1 and its interactions with Tm. The stability predictions made by the model correlated well with the affinity changes observed in vitro of TnT mutants for Tm. The changes in Ca2+ sensitivity showed a strong correlation with the changes in binding affinity. We suggest the primary reason by which these TNNT2 mutations between residues 92 and 144 cause cardiomyopathy is by changing the affinity of TnT for Tm within the TNT1 region.
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