Nanomechanical phenotypes in hypertrophic cardiomyopathy caused by missense mutations in cardiac myosin-binding protein C

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Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac muscle disease, with a 0.2% of global prevalence. This illness is characterized by left ventricular chamber reduction and left ventricular wall hypertrophy, together with hypercontractility and impaired diastole. Despite of its high prevalence, HCM still has no cure, as its heterogeneity difficults the identification of a single underlying pathogenic mechanism[1,2].

We investigate the molecular mechanisms that induce HCM in the 10-20% of patients who carry missense mutations in MYBPC3, the gene coding for cardiac myosin-binding protein C (cMyBP-C)[3]. This is a sarcomeric protein that tethers the actin and the myosin filaments, braking their gliding and tuning muscle contraction[4,5]. We have curated a database of missense variants in MYBPC3 according to their clinical presentation and studied potential drivers of the disease. Using bioinformatics tools, we found that most of the pathogenic variants are not predicted to induce gross changes in thermodynamical stability or RNA splicing. Hence, we hypothesized that pathogenic mutations can alter the mechanical properties of cMyBP-C, leading to reduce braking ability and thus to hypercontractility and HCM. To test this, we have produced several variants of the C3 domain of cMyBP-C, a central domain of the protein without known protein interactors. As expected, most mutants retain close-to-wild-type structure and thermodynamic stability. However, some pathogenic mutants show altered mechanical stability or refolding behaviour, as determined by single-molecule atomic force microscopy experiments in force-clamp mode. This is the first time that pathogenic mutations occurring at C3 are linked to nanomechanical phenotypes, which could affect the tethering function of cMyBP-C and trigger the development of HCM.