Cardiomyopathy can be classified into at least four main forms, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy, and left ventricular noncompaction. HCM produces ventricular wall thickening, especially in the interventricular septum, with decrease in ventricular chamber volumes. DCM produces a prominent increase in chamber volumes without ventricular wall thickening. In HCM, systolic function is increased or at least preserved, whereas diastolic function is impaired in part because of the hypertrophy itself, interstitial fibrosis, and/or myocyte disarrays. Diastolic dysfunction is thought to be responsible for symptoms of heart failure and premature sudden cardiac death of HCM patients. In contrast, DCM is characterized by systolic dysfunction, which leads to congestive heart failure requiring cardiac transplantation. Restrictive cardiomyopathy is characterized by restrictive diastolic dysfunction (restrictive filling and reduced diastolic volume of either or both ventricles) with normal or near normal systolic function and wall thickness. Left ventricular noncompaction is characterized by deep trabeculation in the ventricular wall with systolic and diastolic dysfunction, arrhythmias, and thromboembolic events.

More than 400 mutations that cause HCM, DCM, restrictive cardiomyopathy, and left ventricular noncompaction have been found in the genes for proteins constituting the sarcomere of cardiac muscle in human, including α- and β-myosin heavy chains, α-cardiac actin, cardiac troponin (cTnT), cTnI, cTnC, α-tropomyosin (αTM), cardiac myosin-binding protein-C, cardiac myosin essential light chain, cardiac myosin regulatory light chain, and cardiac titin/connexin.4 Most mutations cause cardiomyopathies in an autosomal dominant manner. Interestingly, the same sarcomeric gene was found to be simultaneously responsible for different forms of cardiomyopathy.4 For example, many mutations in cTnT, cTnC, α-tropomyosin, α-cardiac actin, β-myosin heavy chain, and titin have been found in both HCM and primary DCM that is clearly distinguished from an end-stage diluted phase of HCM. This strongly suggests that the location of mutation, and thus its specific consequences on protein structure and function play an important role in the distinctive phenotypic variation between HCM and DCM. Many mutations in cTnI have also been found in both HCM and restrictive cardiomyopathy. Surprisingly, however, no mutations in cTnI were found to cause autosomal dominant DCM, with only one mutation, A2V, being reported to cause a rare case of DCM inherited in a “recessive” manner.3

In this issue of Circulation Research, Carballo et al3 identified the first mutations in TNNI3 (cTnI gene), K36Q and N185K, to cause autosomal dominant DCM by testing TNNI3 as a candidate gene in a panel of probands with DCM and expanded the spectrum of disease genes that lead to either HCM or DCM depending on the specific mutation. The K36Q mutation is in a postulated hinge region that mediates the movement of the N-terminal region in cTnI on phosphorylation of S22/23 by cAMP-dependent protein kinase. The N185K mutation is in an α-helix of cTnI that binds to actin-tropomyosin. These mutations were each found in small single families with severe and early onset DCM. In the family with the K36Q mutation, the proband and his younger son carrying mutation were diagnosed with severe DCM at age 15 and 6, respectively, with a rapid deterioration requiring early cardiac transplantation. The older son of the proband carrying mutation was diagnosed with mild DCM at the age of 7 on screening. In the family with the N185K mutation, the proband was diagnosed with severe DCM at the age of 24, and 13 months later, he underwent cardiac transplantation. His father was diagnosed with DCM at the age of 50. After 4 years without symptoms, the father required cardiac resynchronization therapy but died from complications. In each family, the mutation identified cosegregated with disease. Unfortunately, the genetic linkage of DCM to these mutations could not exclusively be demonstrated because of the small family sizes, so that they further investigated the functional impacts of these mutations in cTnI in an elegant manner using synthetic thin filaments to obtain additional strong evidence of pathogenicity. They reconstituted thin filaments using physiological stoichiometric amounts of rabbit skeletal muscle actin, recombinant human αTM, and recombinant human cardiac troponin, 7:1:1 respectively. Thin filaments reconstituted with cTnI with the putative DCM mutations conferred decreased maximum activity and Ca²⁺ sensitivity on rabbit skeletal muscle myosin S1 ATPase activity compared to those reconstituted with wild-type cTnI. Furthermore, they showed that the Ca²⁺ binding affinity of the regulatory site II of cTnC was significantly reduced in the thin filament containing mutant cTnIs by using a fluorescently labeled cTnC as a reporter.

These results strongly suggest that both the K36Q and N185K mutations in TNNI3 cause DCM via a similar pathogenic mechanism to the DCM mutations found in other
sarcromeric regulatory proteins. The first cTnT mutation responsible for familial DCM is a deletion mutation, ΔK210, in TNNT2 identified in 2 independent families. This mutation had a Ca\(^{2+}\)-desensitizing effect on the force generation in skinned cardiac muscle fibers and the ATPase activity.\(^6\)\(^7\) The second mutation, R141W, that causes DCM was found in a large family. This mutation also decreases the Ca\(^{2+}\) sensitivity of force generation without changing maximum force-generating capability and cooperativity and unloaded shortening velocity in skinned cardiac muscle fibers.\(^8\) The disease generating capability and cooperativity and unloaded shortening velocity in skinned cardiac muscle fibers.\(^8\) The disease expression of R131W, R205L, and D270N is similar to that of ΔK210 in severity, being characterized by early-onset phenotype, high incidence of sudden death and/or heart failure, and frequently observed cardiomegaly. Functional studies show that reduced Ca\(^{2+}\) sensitivity is a consistent property of these mutations.\(^9\) Knock-in mice, in which 3 base pairs coding for the residue K210 were deleted from endogenous TNNT2 genes using gene-targeting technology, developed enlarged hearts and heart failure and showed a high incidence of premature sudden death,\(^10\) closely recapitulating the clinical phenotypes of human patients.\(^11\)\(^12\) Skinned cardiac muscle fibers from these mice showed a decrease in Ca\(^{2+}\) sensitivity of force generation, and oral administration of pinobendan, known to increase the cardiac myofilament Ca\(^{2+}\) sensitivity, was found to prevent cardiac remodeling and markedly improve the life expectancy, demonstrating that Ca\(^{2+}\) desensitization is a primary functional defect triggering the pathogenesis of DCM associated with the deletion mutation ΔK210 in cTnT. A missense mutation, G159D, in TNNC1 (cTnC gene) was found in a DCM family with a malignant phenotype. This mutation reduced the Ca\(^{2+}\) sensitivity in actomyosin ATPase and in vitro motility assays.\(^9\) Two missense mutations, E40K and E54K, have been identified in the TPM1 (αTnI gene) as a cause of DCM with a relatively malignant phenotype. Both mutations decreased the Ca\(^{2+}\) sensitivity, as demonstrated in studies using reconstituted actomyosin or myofibrillar ATPase activity and the in vitro motility assay.\(^9\)\(^13\) Transgenic mice expressing E54K mouse αTnI showed significant decreases in the cardiac myofilament Ca\(^{2+}\) sensitivity, consistent with the in vitro studies, as well as a marked depression in maximum force cross-sectional area.\(^14\)

In contrast to the DCM-causing mutations, HCM-causing mutations in sarcromeric regulatory proteins have been reported to generally increase the cardiac myofilament Ca\(^{2+}\) sensitivity. Most mutations in cTnT identified in HCM patients increase the Ca\(^{2+}\) sensitivity, without impairing the maximum force-generating capability and ATPase activity.\(^15\)\(^17\) Transgenic mice expressing I79N human cTnT showed increased cardiac myofilament Ca\(^{2+}\) sensitivity.\(^18\)

Transgenic mice expressing R92Q human cTnT showed increased basal sarcomeric activation in cardiac myocytes, impaired relaxation, and shorter sarcomere lengths, indicative of increased Ca\(^{2+}\) sensitivity.\(^19\) A Ca\(^{2+}\)-sensitizing effect on cardiac muscle contraction has also been observed for most mutations in TNNI3 and TPM1 associated with HCM.\(^1\) Transgenic mice expressing R145G cTnT showed a significant increase in myofilament Ca\(^{2+}\) sensitivity with maximum force depression.\(^20\) Transgenic mice expressing E180G αTnI also showed increased myofilament Ca\(^{2+}\) sensitivity.\(^21\)

Collectively, functional studies, which have so far been made on sarcromeric regulatory proteins, demonstrate that HCM-causing mutations generally increase the Ca\(^{2+}\) sensitivity of cardiac myofilament, whereas DCM-causing mutations decrease it, strongly suggesting that these opposite changes in cardiac myofilament Ca\(^{2+}\) sensitivity may play important roles in determining the distinctive phenotypic difference between HCM and DCM, at least associated with the sarcromeric regulatory protein mutations. To elucidate potential therapeutic targets in these diseases, future study should be focused on the detailed molecular mechanisms by which functional consequences of these mutations converge to either Ca\(^{2+}\) sensitization or Ca\(^{2+}\) desensitization of myofilament and on the entire molecular cardiac remodeling pathways by which they ultimately lead to HCM or DCM.

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References


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