Sarcomere Mutations in Cardiomyopathy, Noncompaction, and the Developing Heart

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In this issue of *Circulation*, Klaassen and colleagues describe mutations in the genes encoding myosin heavy chain (MHC), cardiac actin, and troponin T in patients with left ventricular noncompaction (LVNC). LVNC, defined as excessive and unusual trabeculation of the mature left ventricle, is thought to reflect a developmental failure of the heart to form fully the compact myocardium during the later stages of cardiac development. Previously, mutations in sarcomeric genes have been linked extensively to the development of hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM). The finding of similar, but not identical, mutations in patients with LVNC suggests a continuum of cardiomyopathy that includes LVNC and further supports the essential role for normal sarcomere function during cardiac development.

Noncompaction of the ventricular myocardium is characterized by a spongy morphological appearance of the myocardium occurring primarily in the left ventricle and most evident in the apical portion. Noncompaction often is visualized as deep recesses within the thickened apex, and these sinusoids communicate with the ventricular cavity. During heart development, the myocardium is initially trabeculated during a period before coronary artery development and is thought to be an adaptation to provide blood flow to the developing myocardium. The development of the coronary vasculature is associated temporally with the loss of trabeculae and the full maturation of the compact myocardium. Between embryonic weeks 5 and 8, the trabeculae regress as the compact myocardium develops from base to apex. Isolated LVNC is defined as occurring in the absence of other cardiac structural malformation. Nonsyndromic LVNC refers to the absence of other extracardiac developmental disorders. In 2006, the American Heart Association scientific statement on classification of cardiomyopathies reclassified LVNC as an isolated LVNC and notably without HCM or DCM. The cohort was screened for mutations in 6 sarcomere genes: β-MHC (*MYH7*), troponin T (*TNNT2*), troponin I (*TNNI3*), myosin regulatory light chain (*MYL2*), myosin essential light chain (*MYL3*), and cardiac α-actin (*ACTC*).

Eleven of 63 subjects (17%) were found to have heterozygous mutations in 3 different sarcomeric genes. Eight of 11 were in *MYH7*, 2 were in *ACTC*, and 1 was in *TNNT2*. Of the 11 individuals identified with sarcomeric gene mutations, 6 had relatives with LVNC, consistent with familial disease. The remaining 5 had sporadic disease, and in 1 individual, neither parent carried the mutation, indicating a de novo mutation. The age range of presentation was 15 to 60 years, and the clinical constellation of symptoms included arrhythmias, heart failure, and embolic events.

The LVNC-associated mutations in β-MHC clustered so that 6 of 8 mutations were in exons 8 and 9 of *MYH7*. Four of these mutations uniquely affected splicing, and the predicted protein product, if made, includes only the first 25-kDa portion of β-MHC, a region that encodes a fragment of the enzymatically active head region. This peptide may be capable of interfering with the actin-myosin interface. Alternatively, it is possible that missplicing effectively results in an absence of protein so that the haploinsufficiency of *MYH7* may contribute to the development of LVNC. Many HCM-associated mutations have been described in exons 8 and 9 of *MYH7* (http://www.cardiogenomics.org). It is important to determine whether these mutations are more likely to associate with increased trabeculation and potentially an increased embolic risk. Although Klaassen et al describe isolated LVNC associated with the missense mutation E101K, this same mutation was previously reported with apical HCM, suggesting an interrelationship between apical HCM and LVNC.

The Klaassen et al study also describes 2 unrelated LVNC cases, both carrying the same cardiac actin (*ACTC*) gene defect, E101K. The cardiac actin gene was previously implicated in both HCM and DCM and was noted specifically in cardiomyopathy gene mutation carriers with unusual apical thickening and trabeculation. The unusual apical disease led Monserrat and colleagues to screen 247 index cases with HCM, DCM, or LVNC specifically for the *ACTC* E101K gene mutation (166 with HCM, 76 with DCM, 5 with LVNC). The same *ACTC* E101K mutation now found by Klaassen et al was identified in 5 families, all from Galicia, Spain, and consistent with a founder effect. Within the Galician families, there were individuals with apical trabeculation that was independent of apical hypertrophy, as well as individuals meeting criteria for isolated LVNC. Curiously, congenital defects, including ostium secundum, atrial septal...
defect, and ventricular septal defect, were described in several family members, consistent with the idea that sarco-
meric gene mutations can produce cardiac developmental anomalies.

The Clinical Spectrum From Sarcomeric Gene Mutations
Sarcomeric gene mutations link to HCM, DCM, and LVNC. As with most monogenic disease, there is diversity of clinical outcome, only some of which is explained by the precise mutation. Individuals carrying the identical sarco-
meric gene mutation display a phenotypic spectrum that may span from those with early-onset, lethal disease to those without evidence of cardiomyopathy. The expressivity of sarcomeric gene mutations in HCM and DCM affects age of onset, age of heart failure symptoms, and importantly, accompanying arrhythmias. Similarly, LVNC sarcomeric gene mutations have a similar broad range of expressivity. As noted by Klaassen et al, the R243H mutation was found in 4 family members meeting LVNC criteria; the 65-year-old grandmother was found to have asymptomatic LVNC, whereas her grandson was diagnosed with LVNC at 2 years of age. This finding underscores the need for family screen-
ing in LVNC cases.

The variables that alter the phenotypic outcome in these disorders are largely unknown but include environmental factors such as diet and exercise and, importantly, also include many unknown genetic factors. The presence of modifier genes can be associated with protective effects or enhancing effects to mediate a more severe outcome. These genetic modifier loci may fall within genetic pathways similar to the primary genetic defect. For example, the presence of 2 distinct sarcomeric gene mutations occurs rarely but is associated with early-onset severe disease. Finally, nonsense-mediated decay, a process in which the mutant mRNA is preferentially reduced, may account for considerable variability because effectively the amount of mutant RNA and protein may differ substantially among individuals.

The families described by Klaassen et al have isolated LVNC without HCM or DCM. However, it has been established that the genetic spectrum from a single mutation can lead to LVNC or apical HCM within a given family. As mentioned, the identical ACTC mutation can associate with LVNC or cardiomyopathy within the same family. Similarly, the missense MYH7 mutation L301Q was found in an individual with LVNC and DCM whose family history included DCM and congestive heart failure. A second family was identified as having 2 MYH7 missense mutations on the same allele, D545N (exon 16) and D955N (exon 23), resulting in LVNC with DCM-like features. The families reported by Klaassen et al are distinct because they lack HCM and DCM, and this observation may correlate with the high prevalence of splice-site mutations.

Diagnostic limitations can influence the designation of LVNC versus HCM or even DCM because echocardiography can be limited in its ability to delineate trabeculations. Additionally, the findings of LVNC, along with HCM or DCM, within the same family need not implicate a sarco-
meric gene mutation because a mutation in the nuclear membrane gene, LMNA, has been described in families with both LVNC and DCM. LMNA encodes the nuclear membrane proteins lamins A and C. A missense mutation, R190W, was identified in a family in which 1 asymptomatic individual had isolated LVNC and 3 others had DCM.

Developmental Implications
LVNC may be present at birth, consistent with a develop-
mental defect. Because LVNC often is diagnosed later in life, it is frequently unknown at which stage LVNC developed and whether the morphology progressed with time. Symptomatic LVNC in early life, consistent with congenital disease, is typically more severe, as are many forms of pediatric cardiomyopathy. The diagnosis of LVNC, particularly familial LVNC, should warrant screening of relatives even in early life. The morphology of LVNC mirrors the appearance of the early developing heart. During myocardial maturation, the developing endocardium is deeply trabeculated. Obstruction of outflow during this window of heart development may enhance noncompaction because valvar atretic lesions can enhance noncompaction. The putative abnormal force generation that may result from sarcomere mutations, particularly MYH7, is consistent with a requirement of normal force production during this developmental window. Supporting the developmental role of MYH7, an R281T mutation was described in a family with LVNC. Intriguingly, 3 individuals also had associated Epstein anomaly and atrial septal defects. This mutation, similar to 6 of the 8 mutations reported by Klaassen et al, falls near the ATPase active site of MHC. Therefore, a mechanism that unifies chamber septation and morphological regression of the trabeculated myocardium may be developmentally linked through the sarcomere.

Conclusions
There is substantial evidence to place LVNC in the context of other cardiomyopathies. The Klaassen et al study clearly demarcates the role of sarcomeric gene mutations as accounting for a significant percentage of LVNC. The study further highlights the potential familial nature of LVNC and the need to evaluate family members of LVNC patients. It has been estimated that 44% of LVNC patients have familial disease. The reports linking LVNC to other forms of cardiomyopathy indicate that family members should be evaluated not only for HCM or DCM but also for septation defects.

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Disclosures
None.

References


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