Genetic Pathogenesis of Hypertrophic and Dilated Cardiomyopathy

Amanda C. Garfinkel, BA[a], Jonathan G. Seidman, PhD[a], Christine E. Seidman, MD[b,c,d,*]

KEYWORDS

• Hypertrophic cardiomyopathy • Dilated cardiomyopathy • Sarcomere physiology
• Interacting-heads motif

KEY POINTS

- Diastolic dysfunction is the earliest identified biomechanical defect in human hypertrophic cardiomyopathy (HCM), whereas systolic dysfunction is the first sign of pathophysiology in dilated cardiomyopathy (DCM).
- HCM variants produce hypercontractile, poorly relaxing sarcomeres via missense mutations in sarcomere proteins.
- Titin truncating variants, yielding titin haploinsufficiency, are the most common cause of familial DCM.

INTRODUCTION

Sarcomere cardiomyopathies are genetic diseases that perturb contractile function and trigger myocardial remodeling along 2 distinct pathways. Hypertrophic cardiomyopathy (HCM) exhibits left ventricular (LV) hypertrophy with preserved systolic function and impaired relaxation. Dilated cardiomyopathy (DCM) is characterized by increased LV chamber size and systolic dysfunction. The clinical manifestations associated with sarcomere cardiomyopathies, including age of onset, severity and progression of morphologic and hemodynamic abnormalities, patient symptoms, and adverse outcomes, are highly variable: a complexity that likely reflects considerable heterogeneity of causal genes and allelic variants, and the influences of background genotypes, environmental exposures, and lifestyles. Together these factors complicate the interpretation of how particular gene mutations alter cardiac physiology.

The discovery of molecular causes for HCM and DCM has propelled gene-based diagnosis and the identification of young mutation-carriers without overt manifestations of cardiomyopathy. These "genotype-positive, phenotype-negative" individuals, although lacking hypertrophy or dilatation, exhibit cardiac abnormalities that provide insights into the earliest biomechanical defects[1–3] that link pathogenic genotypes to cardiac dysfunction.

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[a] Department of Genetics, Harvard Medical School, New Research Building Room 256, 77 Avenue Louis Pasteur, Boston, MA 02115, USA; [b] Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA; [c] Department of Genetics, Brigham and Women's Hospital, Harvard Medical School, New Research Building Room 256, 77 Avenue Louis Pasteur, Boston, MA 02115, USA; [d] Howard Hughes Medical Institute, 4000 Jones Bridge Road, Chevy Chase, MD 20815, USA
* Corresponding author. Department of Genetics, Harvard Medical School, New Research Building Room 256, 77 Avenue Louis Pasteur, Boston, MA 02115.
E-mail address: cseidman@genetics.med.harvard.edu

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Understanding these early molecular pathophysiologic events can illuminate modifiable pathways to reduce the emergence of overt HCM and DCM and limit adverse patient outcomes. In this review, the authors outline current understandings of how normal sarcomere structure and function are altered by human mutations that cause HCM or DCM.

PROPERTIES OF NORMAL SARCOMERE STRUCTURE AND FUNCTION

Components of the Cardiac Sarcomere

The sarcomere is the basic contractile unit of striated muscle, composed of thick and thin filaments (Fig. 1). Sarcomeres are aligned through Z-discs located at the boundary of each sarcomere and interconnected through particular thick filaments to form muscle fibers. Combined with electrophysiologic machinery, sarcomeres are responsible for contraction and relaxation of all muscle cells.

Sarcomere thin filaments are composed of α-actin (*ACTC1*) filaments and the calcium-sensitive troponin-tropomyosin regulatory apparatus, which includes troponin T (*TNNT2*), troponin I (*TNNI3*), troponin C (*TNNC1*), and α-tropomyosin (*TPM1*).

Sarcomere thick filaments contain proteins with both motor and regulatory functions. Cardiac β-myosin heavy chain (*MYH7*), the molecular motor of the thick filament, contains structural and functional domains. Myosin α-helical tails pack together to form a cylindrical backbone of thick filaments, from which pairs of myosin heads project laterally in a helical fashion at regular intervals. These protruding globular heads (denoted S1) contain a nucleotide-binding pocket with adenosine triphosphate (ATP) hydrolase activity, actin-binding sites, and regulatory domains that interact with the regulatory and essential light chains (RLC and ELC, encoded by *MYL2* and *MYL3* genes, respectively). An S2 fragment links the S1 head to myosin's tail backbone and binds myosin binding protein C (cMyBP-C, encoded by *MYBPC3*) and titin (*TTN*).[4] cMyBP-C binds actin filaments and myosin S2; these interactions are modulated

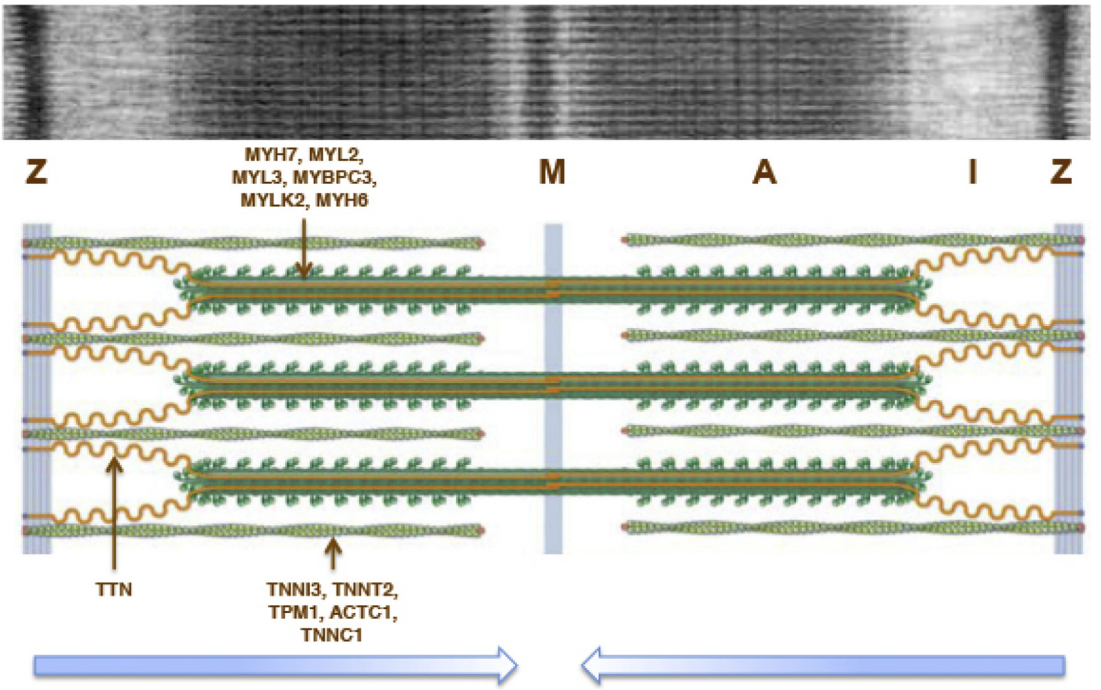

Fig. 1. The sarcomere. Cardiac sarcomeres are composed of highly organized thick and thin myofilaments that produce bands that are visible by microscopy (*top image*). One sarcomere encompasses the region between 2 Z bands, where titin and thin filaments are anchored and interact with other Z-disc proteins. The I band denotes the region lacking thick filament motor proteins that reside in the A band. The M band is an overlap region that interconnects thick filament proteins within each sarcomere. Each titin molecule spans from the Z disc to the M band, encompassing one-half of a sarcomere. The thick filament fulfills motor and regulatory functions through proteins much as cardiac β-myosin heavy chain (*MYH7*) and myosin binding protein C (*MYBPC3*). The thin filament system contains actin as well as the troponin-tropomyosin calcium-regulatory apparatus that enables and regulates actomyosin interactions. Titin(*TTN*) plays multiple roles in sarcomere function, stability, and regulation.