



Review

Epigenetics, Modifiers, and Molecular Noise: Rethinking Pathophysiology in Dilated and Hypertrophic Cardiomyopathies

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Abstract

Cardiomyopathies comprise a heterogeneous group of myocardial disorders characterized by intrinsic structural and functional abnormalities that are not explained by secondary cardiovascular or systemic conditions. Although genetically determined cardiomyopathies have traditionally been interpreted within a Mendelian framework, this paradigm does not fully account for the marked variability in penetrance, expressivity, and clinical outcomes observed in affected individuals. Increasing evidence indicates that disease manifestation arises from a complex interplay between rare pathogenic variants, common genetic variation, epigenetic regulation, environmental factors, and stochastic molecular processes. This review focuses on hypertrophic and dilated cardiomyopathies, the most prevalent and extensively studied forms, and critically examines how epigenetic mechanisms, genetic modifiers, and molecular noise challenge classical pathophysiology concepts. We discuss how these factors contribute to phenotypic heterogeneity and influence disease severity, progression, and therapeutic response. Recognition of this multilayered genetic architecture has important clinical implications, supporting more refined risk stratification, improved genetic counseling, and the development of personalized and potentially variant-agnostic therapeutic strategies.

Keywords: hypertrophic cardiomyopathy; dilated cardiomyopathy; epigenetics; modifier; molecular noise



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