pagepress

GLOBAL CARDIOLOGY
Global Cardiology 2024; **4**
Published online 30 December 2024 | **DOI**: 10.4081/cardio.2024.54

LETTER TO THE EDITOR

Unveiling the genetic aetiology of "non-genetic" dilated cardiomyopathy

Emanuele Monda,[1] Giuseppe Limongelli[1,2]

[1]Inherited and Rare Cardiovascular Diseases, Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Monaldi Hospital, Naples, Italy; [2]Institute of Cardiovascular Science, University College London, London, UK

Abstract

Background: Dilated cardiomyopathy (DCM) is defined by the presence of left ventricular dilation and systolic dysfunction in the absence of coronary artery disease or abnormal loading conditions sufficient to cause global systolic impairment. While this condition has been traditionally classified as genetic and non-genetic, there is increasing evidence that the individual genetic background may eventually increase the susceptibility or act as disease modifier in the presence of an external cause for myocardial dilation and dysfunction.
Methods: A comprehensive literature search was conducted to identify studies describing cohorts of patients with peripartum cardiomyopathy, alcoholic cardiomyopathy, chemotherapy-induced cardiomyopathy, myocarditis, and DCM associated with systemic immune-mediated diseases who systematically underwent genetic testing.
Results: The studies identified showed a high proportion of pathogenic variants in genes associated with cardiomyopathy among patients affected with these conditions. These findings support the emerging 'two-hit' hypothesis, in which the cumulative impact of genetic and environmental risk factors increases the likelihood of developing the disease phenotype.
Conclusions: This perspective summarizes the available data on the role of genetics in predisposing individuals to conditions that lead to a DCM phenotype, which were previously considered to be acquired or environmental.

Key words: dilated cardiomyopathy; peripartum cardiomyopathy; alcoholic cardiomyopathy; chemotherapy; myocarditis; genetics.

Received: 21 August 2024; Accepted: 4 December 2024.
**Correspondence to: Giuseppe Limongelli, MD, PhD, FESC, Inherited and Rare Cardiovascular Disease Clinic, Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli," c/o Monaldi Hospital, AORN Colli, Via L. Bianchi 1, 80131 Naples, Italy. E-mail: limongelli.giuseppe@gmail.com*

Dilated cardiomyopathy (DCM) is defined by the presence of left ventricular (LV) dilation and systolic dysfunction in the absence of coronary artery disease or abnormal loading conditions sufficient to cause global systolic impairment.[1] DCM has been traditionally classified as genetic, caused by deleterious variants in genes encoding structural or functional proteins of the cardiac muscle, and non-genetic, induced by environmental, hormonal, or toxic factors. A comprehensive diagnostic work-up aiming at identifying the underlying cause has been proposed in clinical practice. In this context, the identification of an acquired cause of DCM, such as infectious or cardiotoxic drug exposure or pregnancy, would eventually conclude the diagnostic work-up.

However, there is increasing evidence that the individual genetic background may eventually increase the susceptibility or act as disease modifier in the presence of an external cause for myocardial dilation and dysfunction. Therefore, a shift toward a genetic/environmental paradigm has recently been proposed to explain the phenotypic expression of several previously considered acquired diseases, such as peripartum, alcoholic, or chemotherapy-induced cardiomyopathy, as well as myocarditis and DCM associated with systemic immune-mediated diseases.

A comprehensive literature search was conducted to identify studies describing cohorts of patients with peripartum cardiomyopathy, alcoholic cardiomyopathy, chemotherapy-induced cardiomyopathy, myocarditis, and DCM associated with systemic immune-mediated diseases who systematically un-

derwent genetic testing. The results are presented in Figure 1**,** and the main results are discussed below. Ware *et al*.[2] found truncating variants in DCM genes in 15% of women with peripartum cardiomyopathy and, most notably, 65% of variants occurred in *TTN*, suggesting that peripartum cardiomyopathy shares a genetic predisposition with both familiar and sporadic idiopathic DCM. Similar results were later observed by Goli *et al*.[3] However, a more complex interplay of still underrecognized environmental or genetic factors could probably explain the significant difference between the age at onset of peripartum cardiomyopathy with those of idiopathic DCM (28 years vs. 65 years, respectively).

Similarly, the effect of genotype and alcohol consumption on phenotype in DCM patients has been investigated. Ware *et al.* screened 141 patients with alcoholic cardiomyopathy and 716 with DCM and found a similar prevalence of DCM-associated genes (13.5% *vs* 19.4%, respectively) with a predominant burden of *TTN* truncating variants. In addition, in a multivariate analysis accounting for covariate predictors of baseline LV ejection fraction (LVEF), neither *TTN* truncating variants nor alcohol consumption were significant predictors in isolation, but the combination of *TTN* truncating variant and alcohol consumption was associated with a significant reduction in baseline LVEF compared with those without these characteristics (8.7% absolute reduction).

Finally, Garcia-Pavia *et al*. studied 213 patients with chemotherapy-induced cardiomyopathy and found that genetic variants occurred in 12% of patients.[5] Even in this case, *TTN* truncating variants predominated (7.5% of cases), and their presence was associated with a higher occurrence of heart failure, atrial fibrillation, and impaired myocardial recovery. This study implies that, along with chemotherapy dosage and traditional cardiovascular risk factors, the identification of genetic variants may be helpful in guiding risk stratification for chemotherapy-induced cardiomyopathy development.

Recently, it has been proposed that even DCM-induced myocarditis may eventually uncover a genetic background. Several case series and cohort studies of patients with acute myocarditis have shown that a substantial proportion of patients carry a pathogenic variant in cardiomyopathy-associated genes.[6-13] Of clinical interest, a correlation has been found between the rate of positive genetic testing and the disease presentation. *Lota et al*. performed genetic testing in 336 consecutive adult patients with acute myocarditis and found that 8% carried pathogenic variants in DCM or arrhythmogenic cardiomyopathy genes,[13] with the highest prevalence in patients with severe presentation (up to 16%). Similar results have been observed in children with acute myocarditis. Thus, a recent systematic review and meta-analysis assessed the prevalence of pathogenic variants in cardiomyopathy-associated genes in patients with diagnosis of acute myocarditis,[14] stratifying patients according to age (adult *vs* paediatric) and clinical scenarios: i) complicated myocarditis (i.e., presentation with acute heart failure, reduced LVEF, or life-threatening ventricular arrhythmias); and ii) uncomplicated myocarditis. According to the results, pooled prevalence was 4.2% in uncomplicated myocarditis, whereas for complicated myocarditis, the pooled prevalence was 21.9% and 44.5% in adults and children, respectively. Moreover, there was a correlation between age at onset, clinical scenario, and specific genes affected by pathogenic variant, with variants in desmosomal genes predominant observed in uncomplicated myocarditis, whereas sarcomeric gene variants were more prevalent in complicated myocarditis, especially *TTN* truncating variants. These findings suggest that genetic determinants may predispose to the occurrence of acute myocarditis, and these episodes of myocardial infection and inflammation may eventually favour the progression toward a DCM phenotype in genetically predisposed individuals.

In addition, it has been recently observed that patients with DCM, likely caused by systemic immune-mediated diseases (SIDs), may also have an underlying genetic background. Stroeks *et al.* recently screened two different cohorts of patients with DCM and a SID, highlighting a prevalence of pathogenic variants in cardiomyopathy-associated genes in 17.1% and 20.5%, with *TTN* truncating variants being the most prevalent.[15]

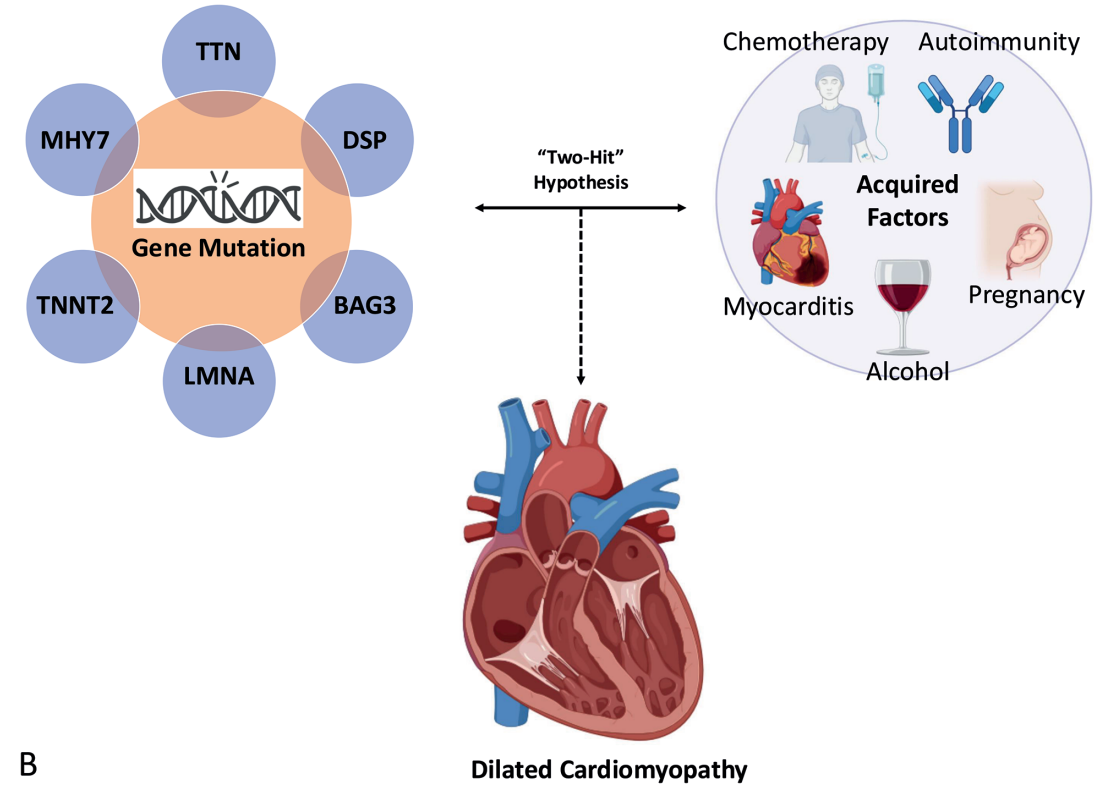
Altogether, these observations lead to the generation of the "two-hits" hypothesis, in which the incremental effect of risk factors (genetic and environmental) increases the likelihood of developing the disease phenotype (Figure 1). Consistent with the concept of the strong genetic/environmental interaction, it has been observed that most patients carrying *TTN* truncating variants have no evidence of cardiac disease, suggesting that cardiac function is preserved in the absence of additional stressors. In this context, hormonal stressor of pregnancy, alcohol, drug use, autoimmunity or myocardial inflammation likely represent such a stressor.

DCM was historically considered the myocardial disease with the lowest diagnostic yield, especially when compared with hypertrophic or arrhythmogenic right ventricular cardiomyopathy. However, the knowledge regarding the causative genes is significantly increasing, along with the broader understanding of disease mechanisms and pathogenesis. Increasing evidence exists to consider genetic testing also in patients with specific causes of DCM previously considered as non-genetic. As discussed above, the yield of genetic testing can be relatively high in these conditions. However, there is limited evidence supporting the systematic testing of all patients with a DCM phenotype, especially in some cases (e.g., patients presenting with diagnosis of myocarditis). Future studies are needed to identify clinical features that may guide genetic testing in these cases.

The identification of genetic determinants has important implications for patients' diagnosis and management, providing insight into the mechanisms of disease development and progression, guiding lifestyle choices and informing clinical follow-up, outcome prediction, risk stratification, and family member screening. Furthermore, emerging therapies for genetic DCM, including gene therapy, will be available in the future.

First Author	Year	Diagnosis	Population (n)	Prevalence (%)	Genetic Variants
Artico et al	2020	Myocarditis (Biopsy-Proven)	36	31	DSP, FLNC, RBM20, TTN
Brown et al	2019	Myocarditis (Clinically Suspected)	8	62	MYBPC3, SCN5A, TNNT2, TTN
Kontorovich et al	2021	Myocarditis (Clinically Suspected or Biopsy-Proven)	117	16	DMD, DNM2, DSP, DYSF, FLNC, MYH7, PKP2, PRDM16, RYR1, SGCG, TRDN, TNNT1, TTN
Lota et al	2022	Myocarditis (Clinically Suspected or Biopsy-Proven)	336	8	BAG3, DES, DSG2, DSP, PKP2, TTN, LMNA, RBM20, TNNC1, TNNT2
Seidel et al	2021	Myocarditis (Biopsy-Proven)	42	21	BAG3, DSP, LMNA, MYH7, TNNI3, TNNT2, TTN
Seidel et al	2022	Myocarditis (Biopsy-Proven)	12	67	MYH7, RYR2, TNNC1, TNNI3, TTN,
Tiron et al	2022	Myocarditis (Clinically Suspected or Biopsy-Proven)	28	18	BAG3, DSP, FLNC, RBM20
van der Meulen et al	2022	Myocarditis (Clinically Suspected or Biopsy-Proven)	7	14	LMNA
Garcia-Pavia et al	2019	Chemotherapy-Induced Cardiomyopathy	213	12	BAG3, LMNA, MYH7, TCAP, TNNT2, TTN
Goli et al	2021	Peripartum Cardiomyopathy	469	15	BAG3, DSP, FKTN, FLNC, ILK, MYH6, MYH7, PLEC, TMPO, TTN, VLC
Ware et al	2016	Peripartum Cardiomyopathy	172	15	DMD, DSP, LAMP2, MYH6, SYNM, TPM1, TTN, VCL
Ware et al	2018	Alcoholic Cardiomyopathy	141	13	BAG3, LMNA, MYH7, TTN
Stroeks et al	2024	Systemic Immune-Mediated Diseases	183	18	BAG3, FLNC, LMNA, MYH7, RBM20, TNNT2, TTN

A



B

Figure 1. A) Summary of the studies investigating the prevalence of pathogenic or likely pathogenic variants in genes associated with cardiomyopathy among patients presenting with myocarditis, chemotherapy-induced cardiomyopathy, peripartum cardiomyopathy, alcoholic cardiomyopathy, and dilated cardiomyopathy associated with systemic immune-mediated diseases. B) Interplay between genetics and environmental factors in determining dilated cardiomyopathy.

Contributions

All the authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare that they have no competing interests, and all authors confirm accuracy.

References

1. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC Guidelines for the management of cardiomyopathies. Eur Heart J 2023;44:3503-3626. doi
2. Ware JS, Li J, Mazaika E, et al. Shared genetic predisposition in peripartum and dilated cardiomyopathies. N Engl J Med 2016;374: 233-41.
3. Goli R, Li J, Brandimarto J, et al. Genetic and phenotypic landscape of peripartum cardiomyopathy. Circulation 2021;143:1852-62.
4. Ware JS, Amor-Salamanca A, Tayal U, et al. Genetic etiology for alcohol-induced cardiac toxicity. J Am Coll Cardiol 2018;71: 2293-302.
5. Garcia-Pavia P, Kim Y, Restrepo-Cordoba MA, et al. Genetic variants associated with cancer therapy-induced cardiomyopathy. Circulation 2019;140:31-41.
6. Artico J, Merlo M, Delcaro G, et al. Lymphocytic myocarditis: a genetically predisposed disease? J Am Coll Cardiol 2020;75: 3098-100.
7. Brown EE, McMilllan KN, Halushka MK, et al. Genetic aetiologies should be considered in paediatric cases of acute heart failure presumed to be myocarditis. Cardiol Young 2019;29:917-21.
8. Kontorovich AR, Patel N, Moscati A, Myopathic cardiac genotypes increase risk for myocarditis. JACC Basic Transl Sci 2021;6:584-92.
9. Seidel F, Holtgrewe M, Al-Wakeel-Marquard N, et al. Pathogenic variants associated with dilated cardiomyopathy predict outcome in pediatric myocarditis. Circ Genom Precis Med 2021;14: e003250.
10. Seidel F, Laser KT, Klingel K, et al. Pathogenic variants in cardiomyopathy disorder genes underlie pediatric myocarditis-Further impact of heterozygous immune disorder gene variants? J Cardiovasc Dev Dis 2022;9:216.
11. Tiron C, Campuzano O, Fernández-Falgueras A, et al. Prevalence of pathogenic variants in cardiomyopathy-associated genes in myocarditis. Circ Genom Precis Med 2022;15:e003408.
12. van der Meulen MH, Herkert JC, den Boer SL, et al. genetic evaluation of a nation-wide Dutch pediatric DCM cohort: the use of genetic testing in risk stratification. Circ Genom Precis Med 2022;15:e002981.
13. Lota AS, Hazebroek MR, Theotokis P, et al. Genetic architecture of acute myocarditis and the overlap with inherited cardiomyopathy. Circulation 2022;146:1123-34.
14. Monda E, Bakalakos A, Cannie D, et al. Prevalence of pathogenic variants in cardiomyopathy-associated genes in acute myocarditis: a systematic review and meta-analysis. JACC Heart Fail 2024;12:1101-11.
15. Stroeks SLVM, Henkens MTHM, Dominguez F, et al. Genetic landscape of patients with dilated cardiomyopathy and a systemic immune-mediated disease. JACC Heart Fail 2024:S2213-1779(24) 00617-6.