Prevalence of Genetic Dilated Cardiomyopathy: A Systematic Literature Review

Michael C. Myers[1], Yue Zhong[1], Sonomi Maruyama[1], Cindy Bueno[1], Arnaud Bastien[1], Boris Breznen[2], Mir Sohail Fazeli[2], Negar Golchin[1]

[1]Bristol Myers Squibb, Princeton, NJ, USA
[2]Evidinno Outcomes Research Inc., Vancouver, BC, Canada

Introduction

- Dilated cardiomyopathy (DCM) is a major cause of heart failure and transplantation,[1] characterized by left ventricular dilatation and reduced ejection fraction (less than 45-50%)[2-5]
- Genetic and acquired factors contribute to DCM; disease-associated genetic variants are found in 20-35% of familial cases.[6] Two of the most common sarcomeric genes frequently associated with DCM etiology are: titin (*TTN*) and myosin heavy chain 7 (*MYH7*)[7]
- DCM prevalence ranges from 1:250 to 1:2500 in the general population.[6,8,9] This corresponds to approximately 0.6 – 1.3 million cases in the United States in 2022

Objectives

- The aim of this review was to synthesize the published literature on the global prevalence of DCM with associated genetic variants (genetic DCM) across various populations, focusing on two of the most common variants: *TTN* and *MYH7*

Methods

- A systematic literature review was conducted by searching MEDLINE® and Embase up to September 19, 2022. Additional searches of relevant conferences within the last two years were conducted, as well as hand searches of previous similar literature reviews
- Included were observational studies reporting the prevalence of genetic DCM within any population; prevalence of *TTN* and *MYH7* mutations were also extracted. Studies using family history as a proxy for genetic DCM or those not published in English were excluded
- Study quality was assessed using the Newcastle-Ottawa scale for observational studies[10] and the Joanna Briggs Institute checklist for cross-sectional studies[11]
- Prevalence was calculated using specific equations (**Figure 1**) for different population groups. Median with interquartile range (IQR) or mean with standard deviation (SD) weighted by sample size (in cases of calculations with <10 studies) were used to summarize the prevalence data

Figure 1. Equations for calculating prevalence of genetic DCM

$$\textit{genetic DCM in total DCM prevalence} = \frac{\textit{Participants with DCM and DCM-associated genetic variant}}{\textit{Participants with DCM}}$$

Equation 1

$$\textit{genetic DCM in general population prevalence} = \frac{\textit{Participants with DCM and DCM-associated genetic variant}}{\textit{Total number in general population}}$$

Equation 2

$$\textit{DCM-associated variants prevalence} = \frac{\textit{Healthy participants with DCM-associated genetic variant}}{\textit{Healthy participants}}$$

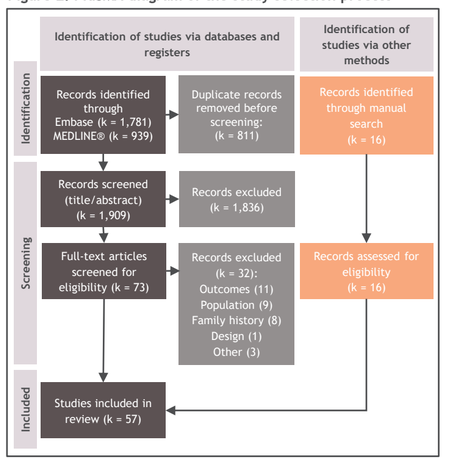
Equation 3

Results

Study and patient characteristics, and study quality

- Of 2,736 records screened, 57 studies were included in the review (**Figure 2**); 31 studies were cross-sectional, 16 were prospective cohorts, and 10 were retrospective cohorts. The top three study countries were the United States (number of studies [k] = 8), the United Kingdom (UK; k = 6), and the Netherlands (k = 6)
- Studies encompassed a total of 481,812 participants (median: 229; range: 21 – 502,462)
- Most studies focused on adult populations, with a median DCM onset age of 45.5 years (range: 0.5 - 57.1 years). The median proportion of female participants was 36.6% (range: 10.7 - 93.5%). Of studies reporting race/ethnicity (k = 17), most participants were White (median: 72.0%)
- Studies were generally moderate to high quality

Figure 2. PRISMA diagram of the study selection process



k – number of records.

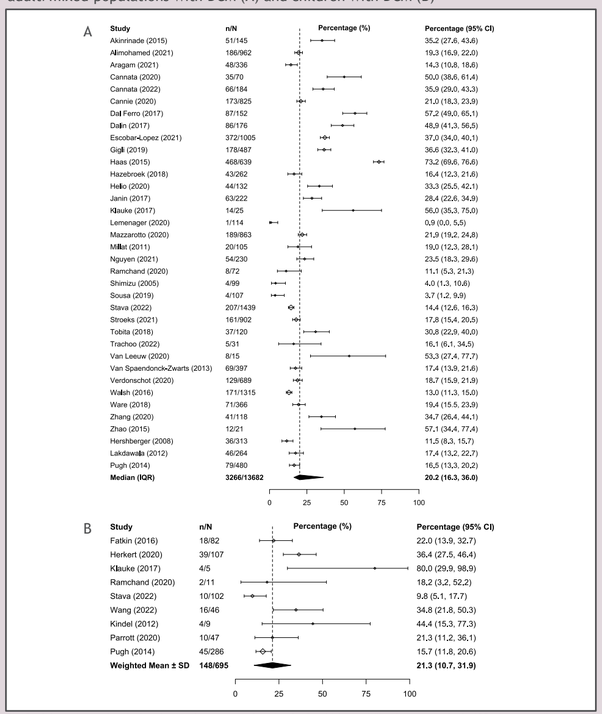
Prevalence of genetic DCM

- Forty-six studies reported on the prevalence of overall genetic DCM, 35 on the prevalence of *TTN*-associated DCM, and 28 on the prevalence of *MYH7*-associated DCM. Gene panels analyzed for overall genetic DCM were heterogeneous

Global median prevalence of genetic DCM was 20.2% (IQR: 16.3 – 36.0%) in the adult DCM population

Global prevalence of overall pediatric genetic DCM within the DCM population was similar (weighted mean: 21.3%)

Figure 3. Median or weighted mean prevalence of overall genetic DCM in adults or adult/mixed populations with DCM (A) and children with DCM (B)



CI – Confidence interval (calculated using the prop.test function for R, which uses Wilson's score method); IQR – Interquartile range; n – Number of genetic dilated cardiomyopathy cases; N – Number of dilated cardiomyopathy cases; SD – Standard deviation.

Overall genetic DCM

- The median prevalence of genetic DCM in adult/mixed (mostly adults with few pediatric patients) populations with DCM was 20.2% (IQR: 16.3 – 36.0%; **Table 1**; **Figure 3A**)
- Prevalence of genetic DCM in children with DCM was 21.3% (weighted mean; SD: 10.6%; **Table 1**; **Figure 3B**)
- Two studies reported the prevalence of adults with genetic DCM within the general population using UK BioBank data. The biobank aims to represent the general population of the UK and includes clinical and genetic information of 500,000 volunteers recruited between 2006 and 2010
  - Using the UK BioBank data at different timepoints, prevalence estimates of genetic DCM ranged from 0.027% to 0.029% among the UK general population

TTN-associated DCM

- Prevalence of *TTN*-associated DCM was 11.4% (median) in adults with DCM and 4.4% (weighted mean; **Table 1**) in children with DCM
- One study reported *TTN*-associated DCM prevalence in general populations, highlighting a significant presence in two distinct cohorts from the UK Biobank (**Table 1**)

MYH7-associated DCM

- *MYH7*-associated DCM prevalence was 3.2% (median) in adult/mixed populations with DCM (**Table 1**) and 5.7% (weighted mean) in children with DCM

Table 1. Prevalence of genetic DCM within the DCM population and the general population, stratified by age group

Group	k	Median prevalence (IQR) / weighted mean prevalence[a] (SD)	Median N (IQR) / total N[b]
Genetic DCM within the DCM population			
Overall genetic DCM	Adult/mixed	36	20.2% (16.3-36.0)	226 (112-525)
	Pediatric	9	21.3% (10.6)	695
TTN-associated DCM	Adult/mixed	30	11.4% (8.2-17.8)	230 (133-492)
	Pediatric	4	4.4% (5.1)	450
MYH7-associated DCM	Adult/mixed	21	3.2% (1.8-5.2)	262 (105-487)
	Pediatric	5	5.7% (4.2)	453
Genetic DCM within the general population			
Overall genetic DCM	Adult/mixed	2	0.029%[c] 0.027%[d]	166,690 18,665
TTN-associated DCM	Adult/mixed	1	Geisinger: 0.04%; PMBB: 0.42%	Geisinger: 92,455; PMBB: 10,289
MYH7-associated DCM	Adult/mixed	-	-	-

[a] Median prevalence and interquartile range are reported unless >10 studies were included in the calculation, in which case a weighted mean and weighted standard deviation were presented. [b] DCM median sample size and interquartile range are reported unless >10 studies were included in the calculation, in which case the total sample size or the individual studies' DCM samples sizes were presented. DCM – Dilated cardiomyopathy; IQR – Interquartile range; k – number of studies reporting; PMBB - PennMedicine Biobank cohort; SD – Weighted standard deviation.

Discussion

- Prevalence estimates of *TTN* and *MYH7* variants were similar to those presented in previous reviews[7,12]
- Previous reviews have estimated that overall genetic DCM accounts for up to 35% of cases.[6] Prevalence of DCM-associated genetic variants could be underestimated in our review as seven studies excluded *TTN* from their cardiomyopathy gene panels, and five studies did not explicitly state the sequenced genes set

Conclusions

- Globally, a significant proportion of adult patients with DCM have genetic factors contributing to disease etiology. Over half of these cases have disease-associated genetic variants in the *TTN* gene and roughly one sixth have variants in the *MYH7* gene
- Current estimates from the literature may be an underestimation of overall genetic factors due to underdiagnosis of earlier stages of DCM and limited genetic screening of DCM patients
- Epidemiological studies using long-read whole genome sequencing and large datasets with genotype-phenotype correlation analyses and complementary functional studies are needed

References

1. Taylor DO, et al. *J Heart Lung Transplant* 2007;26(8):769-781
2. Elliott P, et al. *Eur Heart J* 2008;29(2):270-276
3. Pinto YM, et al. *Eur Heart J* 2016;37(23):1850-1858
4. Burkett EL, et al. *J Am Coll Cardiol* 2005;45(7):969-981
5. Mestroni L, et al. *Eur Heart J* 1999;20(2):93-102
6. Weintraub RG, et al. *Lancet* 2017;390(10092):400-414
7. McNally EM, et al. *Circ Res* 2017;121(7):731-748
8. Hershberger RE, et al. *Nat Rev Cardiol* 2013;10(9):531-547
9. Reichart D, et al. *J Intern Med* 2019;286(4):362-372
10. Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Published 2021. Accessed Dec 20, 2023
11. The Joanna Briggs Institute. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews Checklist for Analytical Cross Sectional Studies. https://jbi.global/critical-appraisal-tools. Published 2020. Accessed Dec 20, 2023
12. Kayvanpour E, et al. *Clin Res Cardiol* 2017;106(2):127-139

Acknowledgements

- This study was funded by Bristol Myers Squibb
- M.C.M., Y.Z., S.M., C.B., A.B., and N.G. are employees and/or shareholders of Bristol Myers Squibb (Princeton, NJ, USA). B.B. and M.S.F. are employed by Evidinno Outcomes Research Inc. (Vancouver, BC, Canada), which was contracted by Bristol Myers Squibb to conduct this study

Email: Michael.Myers@bms.com