The Burden of Dilated Cardiomyopathy Variants in an Adult Cardiac Transplant Bank

Alex Cullen; Max Jason MD; Madelyn Boslough MD; Sharon Graw PhD; Amrut Ambardekar MD; Joe Cleveland MD; Shanshan Gao PhD; Garrett Steed; TOPMed; Luisa Mestroni MD; Matthew R. Taylor MD, PhD

Background: Heart failure (HF) is a leading cause of morbidity and mortality in the U.S., and over 4,500 heart transplants are performed in the U.S. annually.[1] Most common causes of HF are ischemic heart failure (IHF)[2] and dilated cardiomyopathy (DCM).[3] Causative DCM gene variants, leading to HF, can be detected in up to 40% of familial cases.[4] The DCM Gene Curation Expert Panel identified 19 genes with 'high' evidence for their association with developing DCM.[5] Implicated genes include *TTN*, *LMNA*, *BAG3*, *DSP*, and *TNNT2*.

Introduction: We sought to analyze genetic variants in explanted failing hearts from a population of patients undergoing cardiac transplantation. We compared these genetic variants to those in nonfailing (NF) hearts and searched for DCM-related pathogenic or likely pathogenic (P/LP) variants in patients undergoing transplant for IHF. We compared a novel variant identification algorithm with an established algorithm to ascertain its utility.

Methods: Explanted hearts with phenotype and demographic data were collected via the University of Colorado Heart Tissue Bank. Non-failing hearts were defined as physically eligible for transplant but not utilized due to factors such as genetic mismatch or time expiration. Whole genome sequencing (WGS) was done by the Broad Institute, contracted by the NHLBI Trans-Omics for Precision Medicine (TOPMed) program. Fifty-seven genes were studied based on curated genes from the ClinGen program for "DCM" and "arrhythmogenic right ventricular cardiomyopathy." ClinVar divided these into Tier 1 and Tier 2 genes. Variant call files were first analyzed using Genoox's Franklin (FKN) algorithm. FKN classifications were scored as P/LP or variants of uncertain significance (VUS), or they were excluded as benign or likely benign (B/LB). Variants found by a proprietary alternative (CVI) algorithm were adjudicated via ClinVar, gnomAD, and medical literature, with decisions of pathogenicity based on American College of Medical Genetics and American College of Pathology guidelines. Variants with minor allele frequencies >0.01 were excluded, and for *FLNC* and *TTN*, only truncation variants were considered.

Results:

Adult Samples	Nonfailing [n = 164]	Failing [n = 520]	DCM [n = 221]	IHF [n = 234]	PPCM [n = 6]
Age [Range]	mean 49.7 y [19, 75]	mean 52.4 y [19, 78]	mean 50.0 y [20, 78]	mean 56.8 y [30, 77]	mean 39.6 y [23, 62]
Sex (M // F // unknown)	77 // 87 // 0	411 // 103 // 6	170 // 50 // 1	201 // 29 // 4	0 // 6 // 0
White	147	381	156	175	3
Black or African American	4	39	26	6	2
Asian	2	11	4	5	0
American Indian/Alaska Native (%)	2	6	4	2	0
More Than One Race	0	4	3	0	0
Race Other, NA, or Unknown	9	79	28	46	1
Not Hispanic or Latino	128	370	159	157	5
Hispanic or Latino	23	47	26	14	1
Ethnicity NA, Unknown or Unreported	13	103	36	63	0
# (%) Positive for P/LP Variant	3 (1.8%)	112 (21.5%)[2]	77 (34.8%)[4]	17 (7.3%)	1 (16.7%)
# (%) Positive for VUS	49 (29.9%)[1]	173 (33.3%)[3]	82 (37.1%)[5]	70 (29.9%)[6]	3 (50.0%)[7]

Table 1. Adult Demographic Data. DCM: Dilated Cardiomyopathy. IHF: Ischemic Heart Failure. PPCM: Peripartum Cardiomyopathy. ([1]Four samples had 2 VUS; [2]Five samples had 2 P/LP; [3]Thirty-five samples had 2 VUS, three samples had 3 VUS, one sample had 4 VUS; [4]Five samples had 2 P/LP; [5]Nineteen samples had 1 VUS, one sample had 3 VUS; [6]Fourteen samples had 2 VUS, one sample had 3 VUS; [7]One sample had 3 VUS)

34.8% of 221 adult end-stage DCM samples had at least one P/LP variant versus 1.8% for 164 adult NF samples ($p = 2.86 \times 10^{-15}$). 7.3% of 234 adult end-stage IHF samples had at least one P/LP variant versus 1.8% for NF ($p = 0.015$). Comparing the DCM and IHF percentages directly yielded ($p = 3.82 \times 10^{-13}$). Five samples had multiple P/LP variants. Twelve P/LP variants were represented by multiple samples. Missense, nonsense, and frameshift variants comprised most P/LP data, with 3 P/LP nonsense variants identified in the nonfailing population. CVI found frameshift variants missed by FKN, but FKN found splice variants missed by CVI. End-stage samples with TTN variants had a mean transplant age of 47.0 years versus 53.5 years for variant-negative samples ($p = 0.0011$).

Conclusion: Our data shows some consistency with prior studies and some heterogeneity of genes and variants. From these prior studies, P/LP variants were identified in 38.7% of non-ischemic HF transplant samples[6] or in 44.3% of explanted DCM hearts.[7] The genetic basis of DCM has been well established, but genetic contribution to end stage heart disease in patients with IHF is less well understood, and there may be an element of environmental and hereditary overlap in these patients. Variant structure sometimes does not match clinical effect, and it is crucial to understand the role that certain genetic mutations play in phenotypic expression. Variants of uncertain significance (VUS) among end-stage samples should drive future functional studies to better isolate pathogenicity of these and similar variants. Genetic screening of donor hearts may be useful, if feasible, to mitigate HF following transplantation. Two different sifting algorithms (FKN and CVI) suggest utility of both. Rarer HF subtypes such as hypertrophic cardiomyopathy (HCM), valvular cardiomyopathy (VCM), restrictive cardiomyopathy (RCM), congenital heart disease (CHD), myocarditis, and retransplant, as well as pediatric data, deserve future attention because of the limited representation in our sample. To individualize treatment of cardiomyopathy, precision medicine approaches include gene replacement, genome editing, signaling pathway modifiers, modifiers of myofilament function, and metabolism.[8,9,10,11,12] Either of these can become relevant as genetic bases are determined, rendering relevance to this study.

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