SUPPLEMENTAL MATERIAL

Supplemental Table 1. List of Variants

Gene	Variant DNA Sequence Change	Classification	Number of individuals	Number of families
MYH7 (N=77, including 3 subjects with 2nd gene variant)	c.170C>A	Likely Pathogenic*	1	1
	c.746G>A	Pathogenic	3	3
	c.968T>A	Likely Pathogenic	2	1
	c.1012G>A	Likely Pathogenic	3	1
	c.1052A>C	Likely Pathogenic*	1	1
	c.1208G>A	Pathogenic	1	1
	c.1477A>G	Likely Pathogenic	1	1
	c.1491G>T	Likely Pathogenic	3	2
	c.1505A>G	Likely Pathogenic	1	1
	c.1727A>G	Pathogenic/Likely Pathogenic	1	1
	c.1750G>C	Pathogenic	1	1
	c.1816G>A	Pathogenic	3	2
	c.1954A>G	Pathogenic	2	2
	c.1987C>T	Pathogenic/ Likely Pathogenic	3	2
	c.1988G>A	Pathogenic	9	7
	c.2104A>G	Likely Pathogenic	1	1
	c.2146G>A	Pathogenic	1	1
	c.2156G>A	Pathogenic	5	3
	c.2167C>T	Pathogenic	5	1
	c.2191C>T	Pathogenic	4	4
	c.2201A>C	Pathogenic	1	1
	c.2221G>T	Pathogenic	2	1
	c.2334C>G	Pathogenic	1	1
	c.2389G>A	Pathogenic	2	2
	c.2524A>G	Likely Pathogenic	1	1
	c.2544G>C	Likely Pathogenic*	1	1

Gene	Variant DNA Sequence Change	Classification	Number of individuals	Number of families
	c.2555T>C	Likely Pathogenic	1	1
	c.2572C>T	Likely Pathogenic	2	2
	c.2609G>A	Pathogenic	2	1
	c.2681A>G	Pathogenic	1	1
	c.2717A>G	Pathogenic	1	1
	c.2770G>A	Pathogenic	2	2
	c.2788G>A	Pathogenic	2	1
	c.2788G>C	Pathogenic/Likely Pathogenic	1	1
	c.2846A>T	Likely Pathogenic*	2	2
	c.4135G>A	Pathogenic	1	1
	c.4487A>C	Likely pathogenic	1	1
	c.5135G>A	Likely pathogenic	2	1
MYBPC3 (N=109, including 1 subject with 2nd gene variant)	c.172delG	Pathogenic	2	1
	c.177_187delAGAGGGCACAC	Pathogenic	2	1
	c.223G>A	Likely Pathogenic	1	1
	c.436dupA	Pathogenic	2	2
	c.459delC	Pathogenic	2	1
	c.671_673delTGC	Pathogenic	1	1
	c.772G>A	Pathogenic	8	7
	c.821+1G>A	Pathogenic	3	2
	c.927-2A>G	Pathogenic	2	2
	c.927-9G>A	Pathogenic	1	1
	c.1090G>C	Likely pathogenic*	1	1
	c.1153_1168delGTGGAACTGGCTGACC	Pathogenic/ Likely Pathogenic	2	1
	c.1210C>T	Pathogenic	3	3

Gene	Variant DNA Sequence Change	Classification	Number of individuals	Number of families
	c.1310delT	Pathogenic	2	2
	c.1484G>A	Pathogenic	1	1
	c.1504C>T	Pathogenic	4	4
	c.1509C>G	Likely Pathogenic*	2	1
	c.1591G>C	Likely Pathogenic	1	1
	c.1624G>C	Pathogenic	2	1
	c.1678delG	Likely Pathogenic	1	1
	c.1790G>A	Pathogenic	1	1
	c.1892delT	Pathogenic	5	1
	c.1928-2A>G	Pathogenic	6	5
	c.2048G>A	Pathogenic	1	1
	c.2170C>T	Pathogenic	1	1
	c.2308G>A	Pathogenic	5	3
	c.2373_2374insG	Pathogenic	1	1
	c.2374T>C	Likely Pathogenic	2	2
	c.2429G>A	Pathogenic	1	1
	c.2454G>A	Pathogenic	2	2
	c.2490dupT	Pathogenic	2	2
	c.2541C>G	Pathogenic	2	1
	c.2550delC	Pathogenic	1	1
	c.2670G>A	Pathogenic	4	2
	c.2774-2775delAG	Pathogenic	1	1
	c.2827C>T	Pathogenic	1	1
	c.2864_2865delCT	Pathogenic	2	2
	c.2905+1G>A	Pathogenic	2	2
	c.3079delGinsAA	Pathogenic	1	1
	c.3124_3125insAA	Pathogenic	2	1
	c.3192_3193insC	Pathogenic	1	1

Gene	Variant DNA Sequence Change	Classification	Number of individuals	Number of families
	c.3330+2T>C	Pathogenic	1	1
	c.3330+2T>G	Pathogenic	9	7
	c.3330+5G>C	Pathogenic	1	1
	c.3330+1T>G	Likely Pathogenic	3	2
	c.3414dupC	Pathogenic	2	2
	c.3624delC	Pathogenic	1	1
	c.3662delT	Likely Pathogenic	1	1
	c.3697C>T	Pathogenic	2	1
	c.3735delC	Likely Pathogenic	1	1
TNNT2 (N=9, including 1 subject with 2nd gene variant)	c.236T>A	Likely Pathogenic	3	2
	c.274C>T	Likely Pathogenic*	1	1
	c.487_489delGAG	Pathogenic	1	1
	c.821+1G>T	Likely Pathogenic	1	1
	c.832C>T	Likely Pathogenic*	1	1
	c.856C>T	Not in ClinVar	2	1
TNNI3 (N=7)	c.431T>C	Likely Pathogenic	2	1
	c.484C>T	Likely Pathogenic	2	1
	c.592C>G	Likely Pathogenic	3	2
MYL2 (N=2)	c.45_46delCAinsT	Likely Pathogenic	1	1
	c.239C>A	Likely Pathogenic	1	1
MYL3 (N=5)	c.170C>A	Pathogenic	3	2
	c.445A>G	Pathogenic	2	2
TPM1 (N=5)	c.457C>G	Likely Pathogenic	3	1
	c.523G>A	Pathogenic	1	1
	c.673A>G	Likely Pathogenic*	1	1
ACTC (N=3)	c.301G>A	Pathogenic	2	1
	c.889G>T	Pathogenic	1	1

*Variant either not present or reported as of uncertain significance (VUS) in ClinVar but considered likely pathogenic by VANISH review, incorporating private cosegregation data in this cohort and absence from population databases.

Supplemental table 2. Domains and outcome measures for the primary outcome

DOMAIN	COMPONENT OUTCOMES
SERUM BIOMARKERS OF MYOCARDIAL INJURY AND STRESS	High-sensitivity cardiac troponin NT-pro-BNP
CARDIAC MORPHOLOGY	CMR LV mass CMR LA volume CMR end-diastolic volume CMR end-systolic volume Z-score for echocardiographic max LV wall thickness
CARDIAC FUNCTION	Z-score for echocardiographic E' Z-score for echocardiographic S'

CMR; cardiovascular magnetic resonance imaging; LA, left atrial; LV, left ventricular; NT-pro-BNP, N-terminal of the pro brain natriuretic peptide.

Supplemental table 3. Demographics across regions

	US	Canada	Brazil	Denmark	P value*
N (%)	169 (80)	4 (2)	27 (13)	12 (6)	
Primary cohort (%)	137 (81)	4 (100)	27 (100)	10 (83)	
Age (yr)	20.2 (8.8)	14.0 (0.8)	33.6 (8.2)	27.6 (7.8)	<0.001
Female gender (%)	73 (43)	1 (25)	7 (26)	5 (42)	0.276
Race (%)					<0.001
White	162 (96)	4 (100)	25 (93)	12 (100)	
Black	1 (1)	0 (0)	2 (7)	0 (0)	
Other	6 (3)	0 (0)	0 (0)	0 (0)	
NYHA class (%)					
I	164 (97)	3 (75)	19 (70)	12 (100)	0.282
II	5 (3)	1 (25)	8 (30)	0 (0)	
Pathogenic or likely pathogenic variant (%)					0.391
ACTC	2 (1)	0 (0)	0 (0)	1 (8)	
MYBPC3	89 (53)	1 (25)	11 (41)	7 (58)	
MYH7	53 (31)	3 (75)	15 (56)	3 (25)	
MYL2	2 (1)	0 (0)	0 (0)	0 (0)	
MYL3	4 (2)	0 (0)	1 (4)	0 (0)	
TNNI3	7 (4)	0 (0)	0 (0)	0 (0)	
TNNT2	8 (5)	0 (0)	0 (0)	0 (0)	
TPM1	4 (2)	0 (0)	0 (0)	1 (8)	

*: Overall comparison across regions comparing North America (US and Canada due to small sample size in Canada), Brazil and Denmark. Chi-square or Fisher's Exact test for gender, race, NYHA class and genes. ANOVA for Age.