

Supplementary table 2. Genotype-phenotype associations for individual sarcomere protein and related genes, with P-values <0.05. P-values reflect the comparison for proportions or means, between patients with and without a rare variant in a given gene.

Phenotype	Gene	Frequency or mean±standard deviation - Rare variant present	Frequency or mean±standard deviation - Rare variant absent	P-value
Age at initial evaluation (years)	<i>MYBPC3</i>	45.5±14.4	51.0±15.5	8.97x10 ⁻⁶
	<i>MYH7</i>	43.9±15.4	50.5±15.2	1.91x10 ⁻⁵
	<i>TNNT2</i>	43.5±14.7	49.8±15.4	0.031
	<i>CSRP3</i>	56.7±8.1	49.5±15.5	0.006
	<i>VCL</i>	43.2±17.6	49.8±15.3	0.0361
Family history of HCM	<i>MYBPC3</i>	40.4% (86/213)	21.9% (140/640)	2.7x10 ⁻⁷
	<i>MYH7</i>	47.4% (54/114)	23.4% (173/740)	3.06x10 ⁻⁷
LA diameter (mm)	<i>RBM20</i>	40.9±6.8	44.2±7.5	0.00239
MLVWT (mm)	<i>MYBPC3</i>	19.4±4.7	18.2±4.2	0.0005
LV end-diastolic diameter (mm)	<i>MYBPC3</i>	44.8±5.5	46.3±6.0	0.00089
	<i>RBM20</i>	43.6±5.2	46.1±6.0	0.00431
LV end-systolic diameter (mm)	<i>MYBPC3</i>	27.4±6.0	28.8±5.4	0.00512
Fractional shortening (%)	<i>MYBPC3</i>	39.7±8.9	38.2±8.8	0.026
LV systolic dysfunction	<i>TNNI3</i>	15.8% (3/19)	3.2% (26/810)	0.020
ASH pattern	<i>MYBPC3</i>	88.0% (184/209)	71.6% (459/641)	3.75x10 ⁻⁶
	<i>MYH7</i>	89.2% (99/111)	73.6% (544/739)	0.00104
	<i>MYH6</i>	81.2% (56/69)	75.2% (587/781)	0.025
Moderate-severe mitral regurgitation	<i>MYL2</i>	55.6% (5/9)	19.4% (158/814)	0.041
Right ventricular hypertrophy	<i>TNNI3</i>	50% (10/20)	21.6% (174/806)	0.004
LVOTO (>30 mmHg)	<i>TNNI3</i>	10% (2/20)	41.2% (326/792)	0.00465
LVOT gradient (mmHg)	<i>TNNI3</i>	13.1±26.6	34.8±41.3	0.002
Family history of SCD	<i>MYBPC3</i>	28.7% (62/216)	18.3% (120/656)	0.001
	<i>MYH7</i>	31.6% (37/117)	19.2% (145/775)	0.003
	<i>TPM1</i>	62.5% (5/8)	20.5% (177/864)	0.012
BP response to exercise (mmHg)	<i>MYH7</i>	36.6±19.9	50.2±24.4	5.49 x 10 ⁻⁶
BP response to exercise ≤ 20 mmHg	<i>MYH7</i>	22.5% (20/89)	12.6% (72/573)	0.020
	<i>TNNT2</i>	40.9% (9/22)	13.0% (83/640)	0.002
Syncope	<i>MYH7</i>	22.8% (26/114)	15.4% (114/742)	0.045

Implanted cardioverter-defibrillator	<i>MYH7</i>	28.2% (33/117)	19.2% (145/756)	0.027
Myectomy and/or alcohol septal ablation and/or pacemaker implantation for gradient reduction	<i>MYBPC3</i> (splicing variants)	43.1% (22/51)	20.0% (160/799)	3.0×10^{-4}

HCM: hypertrophic cardiomyopathy; NYHA: New York Heart Association; LA: left atria; MLVWT: maximum left ventricular wall thickness; LV: left ventricular; ASH: asymmetric septal hypertrophy; LVOT: left ventricular outflow tract; LVOTO: left ventricular outflow tract obstruction; SCD: sudden cardiac death; BP: blood pressure;