

The American Journal of Human Genetics, Volume 91

Supplemental Data

**Burden of Rare Sarcomere Gene Variants
in the Framingham and Jackson Heart Study Cohorts**

Alexander G. Bick, Jason Flannick, Kaoru Ito, Susan Cheng, Ramachandran S. Vasani, Michael G. Parfenov, Daniel S. Herman, Steven R. DePalma, Namrata Gupta, Stacey B. Gabriel, Birgit H. Funke, Heidi L. Rehm, Emelia J. Benjamin, Jayashri Aragam, Herman A. Taylor Jr., Ervin R. Fox, Christopher Newton-Cheh, Sekar Kathiresan, Christopher J. O'Donnell, James G. Wilson, David M. Altshuler, Joel N. Hirschhorn, J. G. Seidman, Christine Seidman

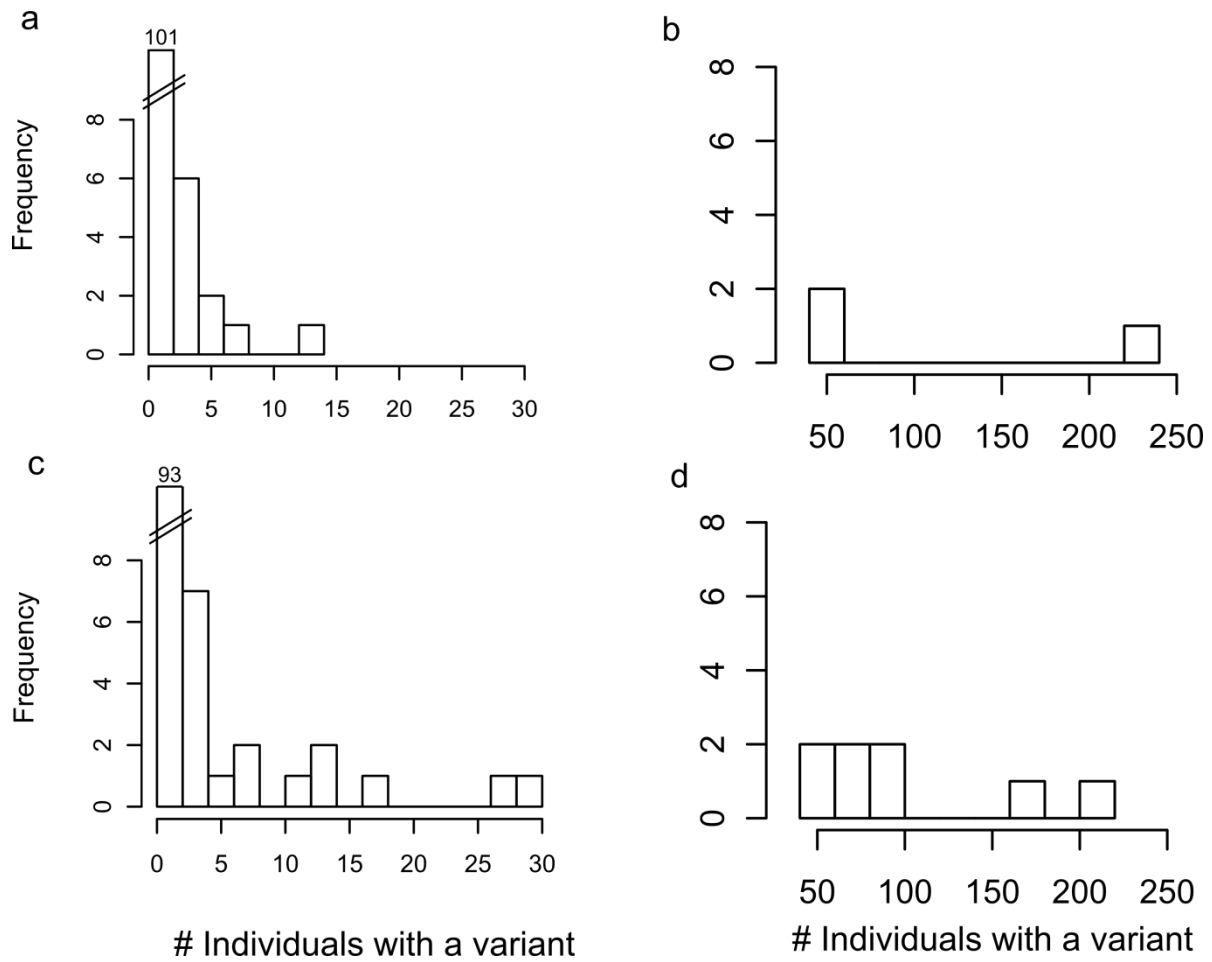


Figure S1. Sarcomere variant allelic frequency spectrum

Histogram of FHS (a,b) and JHS variant distribution (c,d) at MAF <1% (a,c) and MAF between 1% and 10% (b,d).

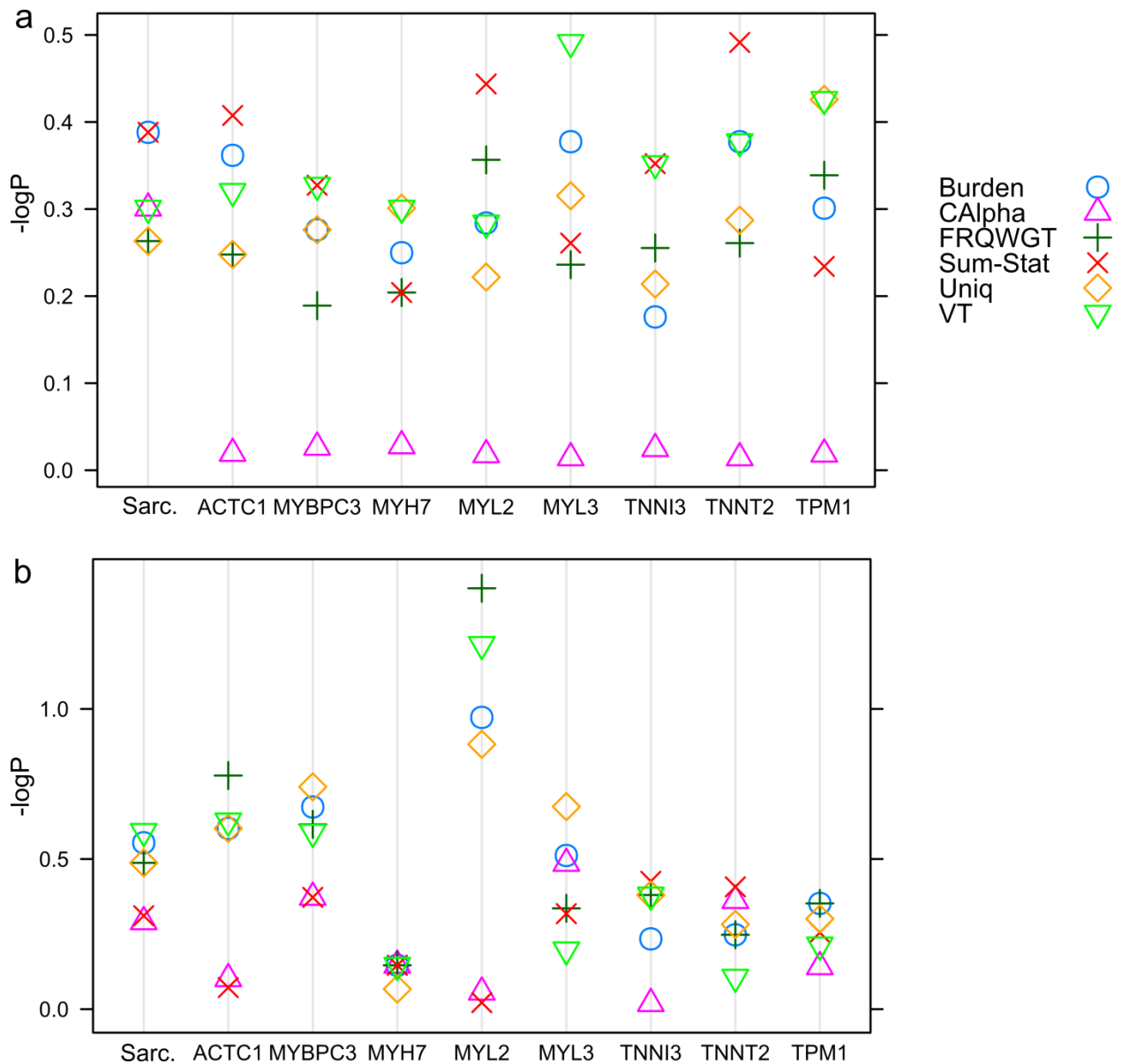


Figure S2. Burden testing of sarcomere variants

Burden testing of sarcomere genes for (a) LVWT and (b) change in LVWT over time in the FHS cohort yields statistically insignificant results ($\log P < 2$) when pooling all of the sarcomere variants (Sarc.) or when considering the eight sarcomere genes individually. Statistical tests computed include burden testing of cases compared to controls (Burden), C-alpha test (CAAlpha), count of case-unique rare alleles (Uniq), variable threshold test (VT), frequency-weighted test (FRQWGT), and sum of single site statistics (Sum-Stat).

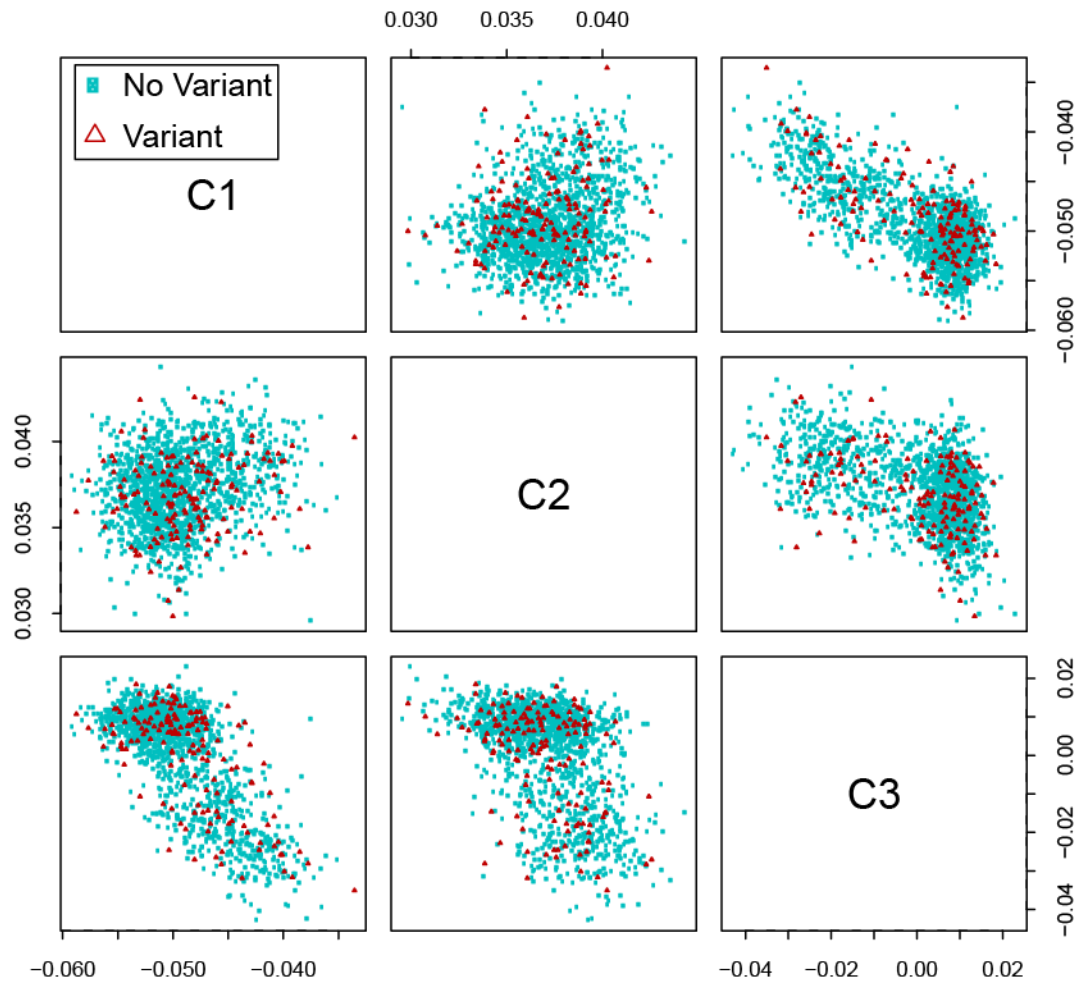


Figure S3. Multidimensional scaling values of FHS rare sarcomere variant carriers

Visual representation of the first three principle components of genetic variation computed based on FHS cohort SNP microarray data illustrates that differences in rare sarcomere variant carrier status was not the result of population stratification resulting from ancestry differences.

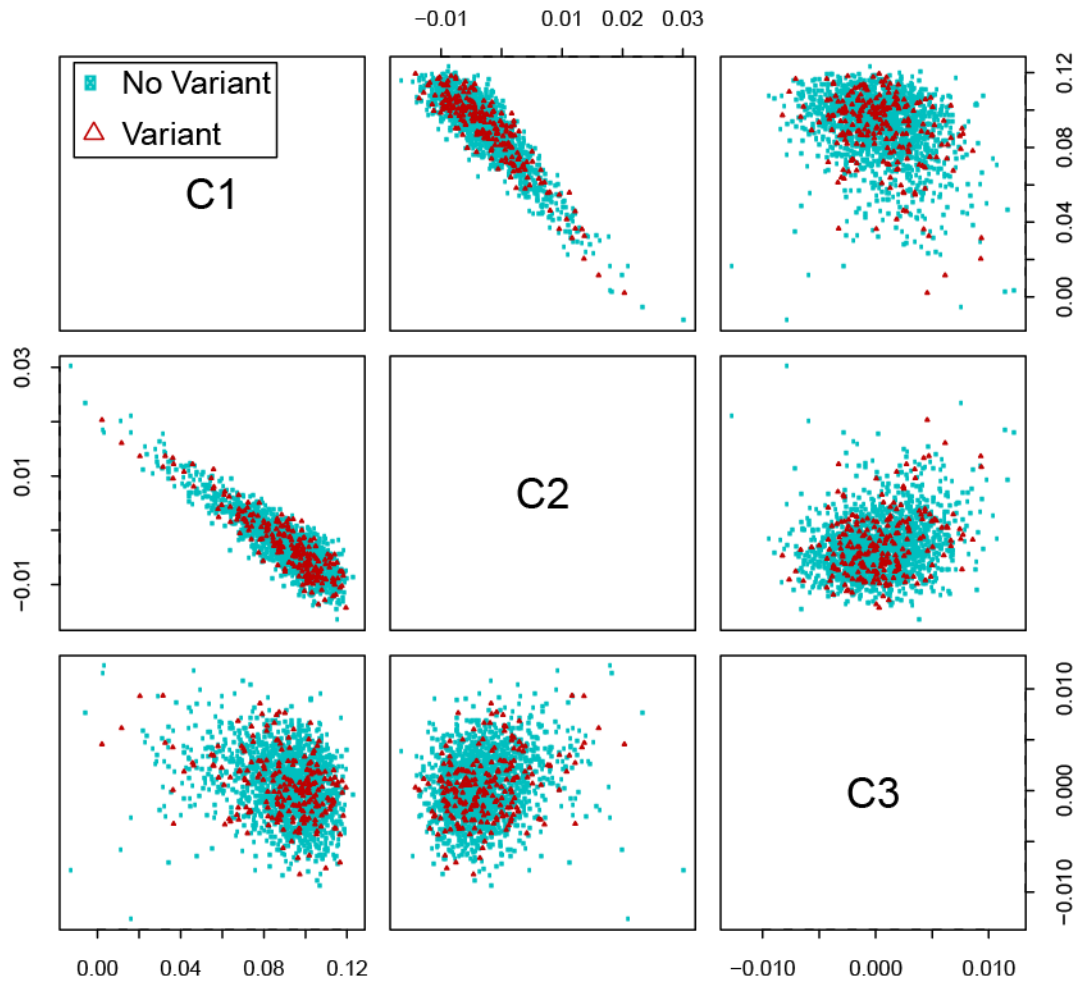


Figure S4. Multidimensional scaling values of JHS rare sarcomere variant carriers

Visual representation of the first three principle components of genetic variation computed based on FJHS cohort SNP microarray data illustrates that differences in rare sarcomere variant carrier status was not the result of population stratification resulting from ancestry differences.

Table S1 List of genes sequenced and quality control metrics

NAME ^a	POS	N EXON	Framingham Heart Study					Jackson Heart Study				
			DENS	RATE	TI TV	BASES 20x	GC	DENS	RATE	TI TV	BASES 20x	GC
<i>ACTC1</i> NM_005159.4	chr15:35082563.. 35088059	6	68.4	0.86	2.08	0.84	0.56	75.4	1.00	2.3	0.99	0.52
<i>MYBPC3</i> NM_000256.3	chr11:47353372.. 47375248	32	62.7	0.93	3.41	0.86	0.63	37.2	0.98	3.8	0.96	0.63
<i>MYH7</i> NM_000257.2	chr14:23882013.. 23903991	38	66.3	0.99	3.10	0.97	0.57	55.4	1.00	3.8	1.00	0.58
<i>MYL2</i> NM_000432.3	chr12:111348831.. 111359383	7	52.4	0.99	3.67	0.97	0.54	30.4	1.00	1.9	1.00	0.54
<i>MYL3</i> NM_000258.2	chr3:46899684.. 46905930	6	56.1	1.00	2.90	0.99	0.59	47.5	1.00	2.1	1.00	0.59
<i>TNNI3</i> NM_000363.4	chr19:55663152.. 55670007	8	54.1	0.93	2.00	0.75	0.61	42.2	0.96	1.8	0.85	0.62
<i>TNNT2</i> NM_001001430.1	chr1:201328288.. 201343432	15	46.5	1.00	3.06	0.96	0.56	42.8	1.00	3.0	0.98	0.57
<i>TPM1</i> NM_001018005.1	chr15:63333979.. 63363421	15	74.0	0.84	1.36	0.67	0.56	47.5	0.88	2.3	0.76	0.53

POS, genomic position. N EXON, number of exons in a gene. DENS, sequencing density. RATE, rate of base calling. TI TV, ratio of the number of transitions to the number of transversions, BASES 20x, fraction of bases with at least 20x coverage. GC, ratio of Guanine to Cytosine bases in a gene.

^aVariant calls made throughout this study are based on the RefSeq gene version indicated.

Table S2. Rare variants (MAF<1%) in eight sarcomere genes identified in FHS participants and their echocardiography data and physiologic risk factors

ID	GENE	LMM	pp HCM	Call	Prot	Age	LVWT	LVDD	LAD	FS	N Phys. Risk Factors
1	<i>MYL2</i>	Likely Path	Path	chr12:111353547C>A	p.Asn47Lys	59	0.88	4.78	4.25	0.35	2
2	<i>MYBPC3</i>	No call	VUS	chr11:47355487C>T	p.Leu994Phe	46	0.82	4.71	3.75	0.38	0
3	<i>MYBPC3</i>	Ben	VUS	chr11:47367871G>A	p.Arg326Gln	49	0.99	4.79	4.2	0.38	1
4	<i>MYL3</i>	VUS	VUS	chr3:46900980G>A	p.Val156Met	68	1.27	4.94	4.44	0.44	1
5	<i>MYH7</i>	No call	Path	chr14:23883232G>A	p.Arg1880His	51	1.02	4.5	3.7	0.37	1
6	<i>MYBPC3</i>	VUS	VUS	chr11:47356691C>T	p.Thr936Met	71	0.96	5.12	3.9	0.39	0
7	<i>MYBPC3</i>	VUS	Ben	chr11:47371619G>A	p.Asp151Asn	61	1.1	4.9	4.49	0.35	2
8	<i>MYBPC3</i>	No call	VUS	chr11:47362770G>A	p.Val60Ile	54	0.94	4.7	3.92	0.29	1
9	<i>MYBPC3</i>	Ben	VUS	chr11:47371592C>T	p.Arg160Trp	67	1.24	4.59	4.05	0.44	0
10	<i>MYH7</i>	No call	Ben	chr14:23898237C>T	p.Ala445Val	64	1.19	4.86	4.64	0.34	2
11	<i>MYBPC3</i>	Path	No call	chr11:47360120G>GA	p.Asn755Gluufs X78	82	1.29	4.99	4.48	0.33	2
12	<i>MYH7</i>	No call	Ben	chr14:23884630G>A	p.Cys1748Tyr	65	0.9	5	3.8	0.4	2
13	<i>MYH7</i>	VUS	Path	chr14:23892910T>C	p.Met982Thr	71	1.03	5.4	3.41	0.44	0
14	<i>MYBPC3</i>	Lik Ben	Ben	chr11:47371330A>G	p.Ser217Gly	53	1.04	5.11	4.31	0.39	2
15	<i>MYL2</i>	VUS	Path	chr12:111348954C>T	p.Pro143Leu	55	0.97	4.89	2.88	0.37	0
16	<i>MYBPC3</i>	Ben	Ben	chr11:47371414G>A	p.Val189Ile	73	1.27	5.44	5.01	0.45	3
17	<i>MYBPC3</i>	Lik Ben	VUS	chr11:47359047G>A	p.Ala833Thr	NA	NA	NA	NA	NA	NA
18	<i>MYBPC3</i>	Ben	Ben	chr11:47371414G>A	p.Val189Ile	50	0.86	4.71	3.52	0.36	0
18	<i>MYH7</i>	No call	VUS	chr14:23887578G>A	p.Arg1337Gln	50	0.86	4.71	3.52	0.36	0
19	<i>MYBPC3</i>	No call	VUS	chr11:47355189C>T	p.Arg1037Cys	57	0.92	4.39	3.54	0.38	0
20	<i>MYBPC3</i>	VUS	Ben	chr11:47372898A>C	p.Thr62Pro	71	0.97	4.41	4.64	0.33	2
20	<i>MYH7</i>	No call	VUS	chr14:23898283G>A	p.Ala430Thr	71	0.97	4.41	4.64	0.33	2
21	<i>MYH7</i>	No call	Path	chr14:23893183G>C	p.Arg952Thr	45	1.11	6.08	3.9	0.3	1
22	<i>MYH7</i>	No call	Path	chr14:23884860G>C	p.Arg1712Pro	56	1.02	4.98	3.78	0.42	1
23	<i>ACTC1</i>	No call	VUS	chr15:35086937G>A	p.Gly25Ser	52	1.16	4.26	3.63	0.45	1
24	<i>MYBPC3</i>	No call	VUS	chr11:47371375A>C	p.Lys202Gln	73	1.09	4.83	4.44	0.31	0
25	<i>MYBPC3</i>	Ben	Ben	chr11:47371414G>A	p.Val189Ile	68	0.99	4.26	4.2	0.37	1
26	<i>MYH7</i>	VUS	Path	chr14:23892910T>C	p.Met982Thr	82	0.97	5	4.35	0.43	NA
27	<i>MYBPC3</i>	VUS	Ben	chr11:47360169C>T	p.Thr737Met	57	1.14	4.28	4.19	0.36	2
28	<i>MYH7</i>	VUS	Path	chr14:23892910T>C	p.Met982Thr	64	1	4.4	4.71	0.48	1
29	<i>MYBPC3</i>	Ben	Ben	chr11:47371414G>A	p.Val189Ile	58	1.13	4.83	4.81	0.37	2
30	<i>MYBPC3</i>	Ben	VUS	chr11:47367871G>A	p.Arg326Gln	52	1.13	5.38	4.38	0.32	3
31	<i>TNNT2</i>	No call	VUS	chr1:201331068T>C	p.Ile221Thr	51	0.95	4.41	3.76	0.38	1
32	<i>MYBPC3</i>	Ben	VUS	chr11:47367871G>A	p.Arg326Gln	72	1	5.7	3.92	0.3	1
33	<i>TPM1</i>	No call	Path	chr15:63353107G>A	p.Arg178Cys	78	1.18	5.79	4.21	0.36	2
34	<i>MYBPC3</i>	Lik Ben	VUS	chr11:47359047G>A	p.Ala833Thr	55	1.02	4.5	3.92	0.4	2
35	<i>MYBPC3</i>	No call	Ben	chr11:47365049G>A	p.Ser406Asn	69	1.11	5.65	3.29	0.43	2
36	<i>MYH7</i>	VUS	VUS	chr14:23886504G>T	p.Lys1459Asn	52	1.1	4.64	4.24	0.37	1
37	<i>MYBPC3</i>	Ben	Ben	chr11:47371414G>A	p.Val189Ile	53	1.09	4.92	4.14	0.34	1
38	<i>MYH7</i>	No call	Path	chr14:23885293A>T	p.Met1625Leu	69	1.13	4.26	3.94	0.46	0
39	<i>MYBPC3</i>	VUS	Ben	chr11:47371355G>C	p.Gln208His	50	0.89	4.81	3.97	0.35	4
40	<i>MYBPC3</i>	VUS	Ben	chr11:47371450C>T	p.Arg177Cys	50	NA	NA	3	NA	1
41	<i>MYBPC3</i>	No call	VUS	chr11:47362736T>G	p.Val617Gly	64	1.06	4.22	4.05	0.36	1
42	<i>MYL3</i>	Likely Path	VUS	chr3:46902303C>G	p.Ala57Gly	69	1.06	4.8	4.34	0.32	0
43	<i>MYBPC3</i>	Ben	Ben	chr11:47371414G>A	p.Val189Ile	73	1.04	4.23	4.25	0.45	2
44	<i>MYH7</i>	No call	VUS	chr14:23894555C>T	p.Arg787Cys	47	1.12	4.45	4.02	0.35	0
45	<i>MYL2</i>	No call	VUS	chr12:111356985GAA AGA>G	p.Lys3Trpfs5X	65	0.99	5.31	3.96	0.4	3
46	<i>MYBPC3</i>	Ben	VUS	chr11:47367871G>A	p.Arg326Gln	46	1.1	5.3	4.31	0.36	4
47	<i>MYBPC3</i>	VUS	Ben	chr11:47371628G>A	p.Gly148Arg	56	1.03	5.17	3.88	0.39	0
48	<i>MYL3</i>	Likely Path	VUS	chr3:46902303C>G	p.Ala57Gly	57	0.9	5.4	3.53	0.33	4
49	<i>MYBPC3</i>	No call	VUS	chr11:47354454G>A	p.Gly1134Asp	65	0.96	5.47	4.11	0.37	1
50	<i>MYL2</i>	Likely Path	Path	chr12:111353547C>A	p.Asn47Lys	58	1.14	4.23	4.11	0.46	0
51	<i>MYBPC3</i>	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	58	1.05	4.6	4.04	0.35	2
52	<i>MYBPC3</i>	VUS	VUS	chr11:47364602G>A	p.Glu441Lys	52	1	4.2	2.8	0.38	1
53	<i>MYBPC3</i>	Ben	Ben	chr11:47371414G>A	p.Val189Ile	48	1.1	5	4.6	0.36	3
54	<i>TNNT2</i>	Ben	Path	chr1:201337340C>T	p.Ala28Val	64	1.56	4.06	3.78	0.41	1
55	<i>MYH7</i>	VUS	Path	chr14:23886807C>T	p.Arg1420Trp	57	1	4.8	4.02	0.29	1
56	<i>MYBPC3</i>	VUS	Ben	chr11:47362731G>A	p.Glu619Lys	65	1.01	4.5	4.28	0.41	2

57	MYBPC3	VUS	Ben	chr11:47356625C>T	p.Thr958Ile	51	1	5.26	4.41	0.25	1
58	MYH7	No call	Path	chr14:23884470A>G	p.Met1765Val	55	0.84	3.8	3.56	0.38	1
59	MYBPC3	VUS	Ben	chr11:47356628C>G	p.Thr957Ser	61	NA	5.4	3.71	0.41	1
60	MYL3	VUS	VUS	chr3:46900980G>A	p.Val156Met	62	0.99	5	3.39	0.44	1
61	MYBPC3	VUS	Ben	chr11:47356628C>G	p.Thr957Ser	65	1.06	4.4	4.09	0.43	0
62	TNNT2	VUS	VUS	chr1:201330453C>T	p.Ala245Val	69	1.07	6.35	4.84	0.19	1
63	MYH7	VUS	VUS	chr14:23899810G>A	p.Val320Met	41	1	4.2	3.83	0.38	0
64	MYH7	No call	Ben	chr14:23883087A>G	p.Thr1891Ala	72	0.98	5.11	4.28	0.41	2
65	MYBPC3	Ben	Ben	chr11:47371414G>A	p.Val189Ile	62	0.72	4.59	3.97	0.37	1
66	MYBPC3	No call	VUS	chr11:47355552G>A	p.Arg972Gln	48	0.9	4.37	2.94	0.35	0
67	MYBPC3	No call	VUS	chr11:47362778T>C	p.Ile603Thr	53	1.05	4.8	5.32	0.37	1
68	MYBPC3	VUS	VUS	chr11:47362758G>C	p.Asp610His	64	1.05	4.9	4.77	0.35	2
69	MYBPC3	VUS	Ben	chr11:47371355G>C	p.Gln208His	68	1.03	4.52	3.85	0.43	2
70	MYBPC3	VUS	VUS	chr11:47364465G>A	p.Arg458His	73	NA	NA	5.4	NA	2
71	MYBPC3	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	51	0.9	4.3	3.1	0.4	1
72	MYH7	Likely Path	Path	chr14:23884256C>T	p.Ser1836Leu	58	0.99	4.87	3.81	0.32	1
73	MYBPC3	No call	VUS	chr11:47355487C>T	p.Leu994Phe	60	1.09	5.21	4.13	0.36	0
74	MYBPC3	VUS	Ben	chr11:47356628C>G	p.Thr957Ser	63	1.14	5.17	4.1	0.3	1
75	MYH7	No call	Path	chr14:23894546G>A	p.Ala790Thr	61	1.22	5.15	3.82	0.32	1
76	MYBPC3	VUS	VUS	chr11:47359115G>A	p.Arg810His	40	1.1	5.4	4.7	0.33	4
77	MYL3	No call	VUS	chr3:46899876A>C	p.Glu186Ala	50	0.82	4.43	3.17	0.39	0
78	MYBPC3	VUS	VUS	chr11:47354463T>C	p.Ile1131Thr	71	0.89	4.95	4.29	0.38	1
79	MYBPC3	VUS	VUS	chr11:47367887G>A	p.Val321Met	60	1.18	5.56	4.35	0.35	0
80	MYBPC3	Ben	VUS	chr11:47367871G>A	p.Arg326Gln	49	0.93	4.98	4.05	0.28	3
81	MYBPC3	Ben	Ben	chr11:47371333G>A	p.Ala216Thr	63	0.89	4.31	3.86	0.32	2
82	MYBPC3	VUS	Ben	chr11:47360169C>T	p.Thr737Met	58	0.84	3.93	3.47	0.35	1
83	MYH7	VUS	Path	chr14:23893148G>C	p.Val964Leu	59	1	4.4	3.43	0.32	1
84	MYBPC3	VUS	VUS	chr11:47363554C>T	p.Ser593Phe	65	1.11	5.49	4.14	0.35	4
85	MYBPC3	VUS	Ben	chr11:47356628C>G	p.Thr957Ser	69	1.14	4.3	3.63	0.32	3
86	MYL3	No call	VUS	chr3:46899949G>A	p.Glu162Lys	72	0.83	4.43	3.95	0.32	4
87	MYBPC3	Lik Ben	Ben	chr11:47371330A>G	p.Ser217Gly	50	0.95	5.42	4.62	0.37	4
88	MYBPC3	No call	VUS	chr11:47371375A>C	p.Lys202Gln	58	1.01	4.66	3.68	0.39	1
89	MYBPC3	Lik Ben	Ben	chr11:47371330A>G	p.Ser217Gly	65	0.87	4.43	3.51	0.39	1
90	MYBPC3	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	82	0.93	5	3.67	0.42	NA
91	MYBPC3	Lik Ben	Ben	chr11:47371330A>G	p.Ser217Gly	54	0.92	4.98	4.1	0.34	4
92	TNNT2	Lik Ben	VUS	chr1:201328767A>G	p.Asn269Asp	58	1.02	5.07	4.61	0.43	1
93	MYBPC3	VUS	Ben	chr11:47371628G>A	p.Gly148Arg	71	1	4.4	3.3	0.39	2
94	MYBPC3	No call	Ben	chr11:47371624C>A	p.Ala149Asp	60	0.95	4.51	4.01	0.35	1
95	MYBPC3	Ben	VUS	chr11:47367871G>A	p.Arg326Gln	55	NA	NA	4.05	NA	3
96	MYBPC3	VUS	Ben	chr11:47372898A>C	p.Thr62Pro	NA	NA	NA	NA	NA	NA
97	MYBPC3	Ben	Ben	chr11:47371414G>A	p.Val189Ile	56	0.88	3.96	3.14	0.47	1
98	MYL3	VUS	VUS	chr3:46899901G>A	p.Asp178Asn	66	0.89	4.4	3.61	0.42	1
99	MYBPC3	Path	Path	chr11:47359280T>C	p.Trp792Arg	53	1.1	4.6	3.1	0.3	1
100	MYBPC3	Ben	Ben	chr11:47371333G>A	p.Ala216Thr	52	0.95	4.62	4.41	0.32	1
101	MYH7	VUS	VUS	chr14:23891398G>A	p.Arg1079Gln	62	0.89	4.78	3.54	0.36	1
102	MYBPC3	Ben	Ben	chr11:47371414G>A	p.Val189Ile	53	0.82	4.73	4.35	0.35	0
103	TPM1	No call	VUS	chr15:6353920G>A	p.Ala191Val	54	1.02	4.66	3.66	0.38	3
104	MYBPC3	VUS	Ben	chr11:47360169C>T	p.Thr737Met	38	1	5	4.05	0.36	3
105	MYH7	No call	No call	chr14:23886827C>A	p.Ser1413*	46	1	5.51	4.92	0.4	1
106	MYBPC3	VUS	VUS	chr11:47364285G>A	p.Gly490Arg	57	1.05	5.22	4.3	0.38	4
107	MYBPC3	VUS	Ben	chr11:47356625C>T	p.Thr958Ile	54	0.97	4.6	3.69	0.42	1
108	TNNT2	Lik Path	VUS	chr1:201334755G>A	p.Glu83Lys	51	0.89	4.34	3.73	0.4	1
109	TNNT2	VUS	No call	chr1:201332519C>T	p.Arg159*	56	0.98	4.04	3.25	0.31	0
110	MYH7	VUS	Path	chr14:23894085C>T	p.Arg858Cys	48	0.95	4.07	3.23	0.43	0
111	MYBPC3	Ben	VUS	chr11:47367871G>A	p.Arg326Gln	63	0.99	4.58	4.04	0.35	1
112	MYBPC3	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	51	1	5.1	3.76	0.37	3
113	MYL2	VUS	VUS	chr12:111356964G>A	p.Ala13Thr	52	0.93	4.73	4.2	0.34	2
114	MYL2	Likely Path	Path	chr12:111350901A>C	p.Glu134Ala	80	1.06	4.59	3.46	0.33	1
115	MYBPC3	VUS	VUS	chr11:47354463T>C	p.Ile1131Thr	64	1.11	5	4.24	0.28	4
116	MYL3	VUS	VUS	chr3:46900985G>A	p.Arg154His	48	1.04	4.43	3.87	0.35	0
117	MYBPC3	VUS	VUS	chr11:47354471G>C	p.Glu1128Asp	58	1.05	4.9	4.01	0.31	0
118	MYH7	No call	Path	chr14:23894557C>T	p.Thr786Met	70	1.1	5.8	5.06	0.38	2
119	MYL3	VUS	VUS	chr3:46900985G>A	p.Arg154His	60	0.89	4.64	4.16	0.38	1
120	MYBPC3	Path	VUS	chr11:47364249C>T	p.Arg502Trp	71	1.07	6.25	3.86	0.17	1
121	MYBPC3	No call	VUS	chr11:47354752A>C	p.Lys1108Thr	76	0.8	4.7	4.63	NA	1
122	MYL3	VUS	VUS	chr3:46899901G>A	p.Asp178Asn	58	1.19	4.85	3.91	0.4	0
123	MYBPC3	No call	VUS	chr11:47355529C>T	p.Arg980Cys	45	1.07	5.34	4.44	0.31	3
124	MYBPC3	VUS	Ben	chr11:47356628C>G	p.Thr957Ser	64	1.01	4.29	4.2	0.43	1
125	MYH7	VUS	Path	chr14:23892910T>C	p.Met982Thr	67	1.05	5.88	4.56	0.22	2
126	MYBPC3	No call	Ben	chr11:47355191G>A	p.Arg1036His	56	0.96	4.67	3.3	0.43	3

127	<i>MYBPC3</i>	Ben	Ben	chr11:47371414G>A	p.Val189Ile	67	0.8	5.84	4.54	0.33	1
128	<i>MYH7</i>	No call	Path	chr14:23883284C>T	p.Arg1863Trp	68	1.25	5.05	4.61	0.33	3
129	<i>ACTC1</i>	No call	VUS	chr15:35086991A>T	p.Thr7Ser	62	1.07	4.4	3.97	0.36	3
130	<i>MYBPC3</i>	Lik Ben	VUS	chr11:47359047G>A	p.Ala833Thr	68	1.05	5.97	4.25	0.35	2
131	<i>MYH7</i>	No call	Path	chr14:23886083G>T	p.Glu1546Asp	54	0.85	4.6	3.9	0.28	1
132	<i>MYBPC3</i>	VUS	VUS	chr11:47353755C>T	p.Arg1228Cys	53	0.8	5.3	4.1	0.4	2
133	<i>MYL3</i>	No call	VUS	chr3:46899876A>C	p.Glu186Ala	65	1.1	5	4.25	0.4	4
134	<i>MYBPC3</i>	No call	VUS	chr11:47354130G>A	p.Arg1205Gln	66	0.8	4.66	3.69	0.37	0
135	<i>MYBPC3</i>	VUS	Ben	chr11:47361309C>T	p.Arg654Cys	44	1	4.5	3.6	0.33	0
136	<i>MYH7</i>	No call	Path	chr14:23883232G>A	p.Arg1880His	52	1.1	5.98	3.7	0.43	1
137	<i>MYBPC3</i>	Lik Ben	VUS	chr11:47359047G>A	p.Ala833Thr	47	0.9	5.4	4.24	0.22	0
138	<i>MYBPC3</i>	Ben	VUS	chr11:47367871G>A	p.Arg326Gln	63	1.08	5.15	4.67	0.34	5
139	<i>MYH7</i>	No call	No call	chr14:23889445A>C	SPLICE SITE	53	0.8	4.64	3.31	0.3	0
140	<i>MYH7</i>	No call	Path	chr14:23887512G>A	ACCEPTOR	58	0.71	4.9	3.79	0.43	0
141	<i>TPM1</i>	No call	Path	chr15:63354775C>T	p.Arg1359His	65	0.84	4.52	3.02	0.37	2
142	<i>MYBPC3</i>	Ben	Ben	chr11:47371414G>A	p.Ala235Thr	75	1.26	4.96	5.04	0.38	3
143	<i>MYH7</i>	VUS	Ben	chr14:23885257G>A	p.Val189Ile	76	0.96	5.82	5.03	0.31	3
144	<i>MYBPC3</i>	Path	No call	chr11:47373058A>G	p.Ala1637Thr	75	1.02	4.9	4.45	0.36	4
145	<i>TNNI3</i>	Path	VUS	chr19:55665462G>A	SPLICE SITE	52	NA	NA	4.1	NA	NA
146	<i>MYL3</i>	VUS	VUS	chr3:46900980G>A	ACCEPTOR	67	1.38	4.49	4.32	0.51	3
147	<i>MYH7</i>	VUS	Ben	chr14:23887536C>T	p.Val156Met	43	0.96	5.45	4.54	0.34	1
148	<i>MYBPC3</i>	No call	VUS	chr11:47361250C>G	p.Thr1351Met	57	1.15	4.9	3.93	0.47	2
149	<i>MYH7</i>	No call	VUS	chr14:23893273T>C	p.Ile673Met	55	0.88	4.77	3.7	0.32	0
150	<i>MYH7</i>	Likely Path	Path	chr14:23884476G>A	p.Met922Thr	54	1.05	4.71	4.34	0.31	1
151	<i>MYBPC3</i>	No call	Ben	chr11:47355128C>T	p.Ala1763Thr	42	0.87	4.63	4.25	0.32	2
152	<i>MYBPC3</i>	VUS	VUS	chr11:47353755C>T	p.Thr1057Met	46	0.9	4.4	3	0.39	1
153	<i>MYH7</i>	No call	Ben	chr14:23896910T>C	p.Arg1228Cys	73	1.01	5.32	3.78	0.26	2
154	<i>MYL2</i>	Likely Path	Path	chr12:111353547C>A	p.Ile591Thr	63	1.19	4.75	4.28	0.38	1
155	<i>MYBPC3</i>	VUS	VUS	chr11:47362772A>G	p.Asn47Lys	53	0.84	4.88	3.16	0.34	0
156	<i>MYBPC3</i>	VUS	Ben	chr11:47356628C>G	p.Asp605Gly	65	0.73	4.66	3.5	0.34	1
157	<i>MYH7</i>	VUS	Path	chr14:23892910T>C	p.Thr957Ser	69	1.06	4.21	3.91	0.41	2
158	<i>TNNI3</i>	No call	No call	chr19:55666189C>T	p.Met982Thr	71	1	4.8	3.79	0.38	1
					p.Arg98*						

ID, participants with sarcomere variants were numbered consecutively. LMM, variant call using the Laboratory for Molecular Medicine database. ppHCM, variant call using the polyphen HCM algorithm. Prot, protein change. LVWT, left ventricular wall thickness (in cm). LVDD, left ventricular diastolic diameter (in cm). LAD, left atrial diameter (in cm). FS, Fractional shortening. NA indicates that the data was not available for our analysis. N Phys. Risk Factors, the number of physiologic risk factors an individual has including hyperlipidemia, hypertension, obesity and diabetes.

Table S3. Rare variants (MAF<1%) in eight sarcomere genes identified in JHS participants and their echocardiography data and number of physiologic risk factors

ID	GENE	LMM	ppHCM	Call	Prot	AGE	LVWT	LVDD	LAD	FS	N Phys. Risk Factors
1	MYBPC3	No call	VUS	chr11:47360202G>A	p.Arg726His	67	0.83	4.93	3.56	0.42	3
1	MYBPC3	Ben	Ben	chr11:47355192C>T	p.Arg1036Cys	67	0.83	4.93	3.56	0.42	3
2	MYBPC3	Ben	Ben	chr11:47371333G>A	p.Ala216Thr	62	0.7	4.8	3.1	0.33	2
2	MYH7	No call	VUS	chr14:23893999C>A	p.Asp886Glu	62	0.7	4.8	3.1	0.33	2
3	MYBPC3	VUS	VUS	chr11:47369411G>A	p.Arg273His	65	1	5.1	3.8	0.45	0
3	MYH7	Ben	Ben	chr14:23886409C>G	p.Ser1491Cys	65	1	5.1	3.8	0.45	0
4	MYBPC3	No call	Ben	chr11:47369995A>T	p.Asn251Ile	61	0.95	5	3.36	0.31	0
5	MYBPC3	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	65	1.1	5.37	3.49	0.5	0
6	MYH7	No call	Path	chr14:23893251G>C	p.Glu929Asp	59	1.13	5.42	3.69	0.32	3
7	MYBPC3	VUS	VUS	chr11:47364209A>G	p.Asn515Ser	62	0.98	4.21	3.65	0.37	2
8	MYBPC3	VUS	VUS	chr11:47354463T>C	p.Ile1131Thr	63	0.96	4.37	3.29	0.41	4
9	MYBPC3	VUS	VUS	chr11:47355553C>T	p.Arg972Trp	61	0.92	5.01	3.77	0.4	2
10	MYBPC3	Ben	Ben	chr11:47357479G>A	p.Val896Met	69	0.68	4.78	3.78	0.4	0
11	MYBPC3	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	74	1	4	2.5	0.43	1
12	MYBPC3	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	72	1	4.2	3.5	0.31	0
12	MYBPC3	No call	Ben	chr11:47356682G>C	p.Arg939Pro	72	1	4.2	3.5	0.31	0
13	MYH7	Ben	Ben	chr14:23886409C>G	p.Ser1491Cys	75	1.1	4.7	2.6	0.47	2
14	MYBPC3	Ben	Ben	chr11:47355192C>T	p.Arg1036Cys	61	NA	NA	NA	NA	1
15	MYH7	VUS	Path	chr14:23892910T>C	p.Met982Thr	68	0.9	4.6	3.6	0.37	0
15	MYBPC3	No call	VUS	chr11:47355528G>A	p.Arg980His	68	0.9	4.6	3.6	0.37	0
16	TPM1	No call	VUS	chr15:63356304G>A	p.Glu272Lys	68	1.3	5	3.8	0.3	1
17	MYBPC3	No call	Path	chr11:47371406G>T	p.Trp191Cys	71	0.87	5.55	4.55	0.34	2
18	TPM1	No call	Path	chr15:63356287A>G	p.Lys266Arg	76	1.1	5.1	3.2	0.25	3
18	MYL3	No call	NA	chr3:46904834C>T	p.Ala16Val	76	1.1	5.1	3.2	0.25	3
19	MYBPC3	No call	VUS	chr11:47365113G>A	p.Val385Met	64	0.9	4.56	3.59	0.38	1
20	MYH7	Ben	Ben	chr14:23886409C>G	p.Ser1491Cys	67	0.97	4.62	3.63	0.41	3
21	MYBPC3	VUS	VUS	chr11:47364209A>G	p.Asn515Ser	74	1.1	5.5	4.3	0.4	2
22	MYBPC3	No call	VUS	chr11:47360202G>A	p.Arg726His	68	1	4.9	3.2	0.31	1
22	MYBPC3	Ben	Ben	chr11:47355192C>T	p.Arg1036Cys	68	1	4.9	3.2	0.31	1
23	MYBPC3	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	61	0.9	5.9	4.1	0.41	4
24	MYBPC3	No call	Ben	chr11:47356733G>A	p.Gly922Glu	69	1.3	5.1	4.04	0.44	3
25	MYBPC3	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	64	0.95	4.73	3.69	0.46	4
26	MYBPC3	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	64	1	4.9	3.4	0.47	3
27	MYBPC3	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	74	1.1	5.2	4	0.38	1
28	TPM1	No call	Path	chr15:63356287A>G	p.Lys266Arg	64	NA	NA	NA	NA	0
29	MYBPC3	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	66	1.3	4.5	3.5	0.4	3
30	MYH7	VUS	Ben	chr14:23885257G>A	p.Ala1637Thr	69	1.06	4.94	4.15	0.39	2
31	MYBPC3	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	71	1.2	4.3	3.9	0.3	3
32	MYBPC3	VUS	VUS	chr11:47364637C>T	p.Ala429Val	63	1.25	4.83	4.03	0.45	4
33	MYBPC3	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	58	1.2	5.2	3.1	0.4	0
34	MYBPC3	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	66	1.4	5.3	3.2	0.34	2
35	MYBPC3	No call	VUS	chr11:47353755C>T	p.Arg1228Cys	58	0.99	4.9	3.33	0.47	3
36	MYH7	Ben	Ben	chr14:23886409C>G	p.Ser1491Cys	74	0.72	4.26	3.54	0.46	3
37	MYBPC3	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	61	0.77	4.83	3.09	0.51	1
38	MYBPC3	No call	Ben	chr11:47356638G>A	p.Ala954Thr	58	1	5.4	3.5	0.46	0
39	MYBPC3	Ben	VUS	chr11:47354442G>A	p.Arg1138His	62	0.79	4.93	3.63	0.45	4
40	MYBPC3	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	67	1	4.87	3.63	0.41	1
41	MYBPC3	Ben	VUS	chr11:47363699C>A	p.Leu545Met	69	0.85	4.32	3.52	0.43	2
41	MYBPC3	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	69	0.85	4.32	3.52	0.43	2
42	MYBPC3	No call	VUS	chr11:47353755C>T	p.Arg1228Cys	71	0.95	4.45	2.74	0.45	3
43	MYBPC3	No call	VUS	chr11:47354846G>T	p.Ala1077Ser	59	0.89	3.89	3.16	0.44	2
44	MYBPC3	VUS	VUS	chr11:47355553C>T	p.Arg972Trp	74	1.07	4.75	NA	0.36	5
45	MYL3	No call	No call	chr3:46901035	FRAME_SHIFT	68	1.15	4.31	3.77	0.47	4

46	<i>MYBPC3</i>	No call	Ben	chr11:47372975C>A	p.Ala36Glu	60	NA	NA	NA	NA	3
47	<i>MYBPC3</i>	No call	VUS	chr11:47371422C>T	p.Pro186Leu	67	1.06	4.46	4.03	0.41	2
48	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	60	1.16	5.21	3.34	0.46	3
49	<i>MYBPC3</i>	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	62	0.93	4.98	3.71	0.45	2
50	<i>MYBPC3</i>	Ben	Ben	chr11:47355192C>T	p.Arg1036Cys	63	1.05	5.47	3.54	0.42	3
51	<i>MYBPC3</i>	VUS	VUS	chr11:47355553C>T	p.Arg972Trp	61	1.11	4.65	3.65	0.46	2
52	<i>TNNT2</i>	Likely Path	Path	chr1:201328373C>T	p.Arg278Cys	64	0.96	4.6	3.89	0.5	2
53	<i>MYH7</i>	No call	Ben	chr14:23897768G>A	p.Glu507Lys	69	0.88	5.31	3.93	0.28	1
54	<i>MYBPC3</i>	VUS	VUS	chr11:47354463T>C	p.Ile1131Thr	66	0.95	4.63	4.07	0.36	0
55	<i>MYBPC3</i>	Ben	Ben	chr11:47355192C>T	p.Arg1036Cys	60	0.78	4.34	3.54	0.38	1
56	<i>MYH7</i>	Ben	Ben	chr14:23886409C>G	p.Ser1491Cys	65	0.87	5.32	3.96	0.39	1
57	<i>MYBPC3</i>	VUS	VUS	chr11:47355553C>T	p.Arg972Trp	75	0.74	5.85	4.23	0.38	2
58	<i>MYBPC3</i>	VUS	VUS	chr11:47364637C>T	p.Ala429Val	67	0.94	4.81	3.27	0.37	2
59	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	74	1.06	4.61	4.45	0.33	2
60	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	62	0.97	4.54	3.34	0.48	1
61	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	64	0.98	6.28	4.3	0.13	2
62	<i>MYBPC3</i>	VUS	VUS	chr11:47355553C>T	p.Arg972Trp	68	0.84	5.05	3.56	0.4	3
63	<i>MYBPC3</i>	Ben	Ben	chr11:47371414G>A	p.Val189Ile	76	0.83	4.33	3.27	0.45	1
64	<i>MYBPC3</i>	VUS	VUS	chr11:47355553C>T	p.Arg972Trp	73	0.83	5.19	3.9	0.38	2
65	<i>MYBPC3</i>	Ben	Ben	chr11:47355192C>T	p.Arg1036Cys	71	NA	NA	NA	NA	0
66	<i>MYBPC3</i>	No call	Ben	chr11:47353650C>T	p.Arg1263Trp	62	0.98	4.32	2.68	0.48	1
67	<i>MYBPC3</i>	No call	Ben	chr11:47364188C>T	p.Ala522Val	61	1.06	4.94	2.86	0.43	2
68	<i>MYH7</i>	VUS	No call	chr14:23902782C>T	p.Arg54*	67	0.78	4.53	3.18	0.41	1
69	<i>MYBPC3</i>	VUS	Ben	chr11:47360169C>T	p.Thr737Met	67	0.96	3.94	3.33	0.42	2
70	<i>MYH7</i>	No call	Path	chr14:23902851T>C	p.Phe31Leu	79	0.71	4.68	3.38	0.42	1
71	<i>MYBPC3</i>	VUS	VUS	chr11:47355553C>T	p.Arg972Trp	62	0.93	4.94	3.81	0.41	3
72	<i>MYBPC3</i>	Ben	Ben	chr11:47357479G>A	p.Val896Met	74	0.89	4.6	3.33	0.29	0
73	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	66	0.92	4.65	3.29	0.43	1
74	<i>TNNT2</i>	No call	Path	chr1:201333428G>A	p.Ala153Thr	66	0.84	4.65	2.85	0.24	1
75	<i>MYH7</i>	VUS	Path	chr14:23892910T>C	p.Met982Thr	61	0.83	4.46	2.98	0.34	3
76	<i>MYBPC3</i>	VUS	VUS	chr11:47355553C>T	p.Arg972Trp	57	0.81	4.93	3.65	0.38	5
77	<i>MYH7</i>	Ben	Ben	chr14:23886409C>G	p.Ser1491Cys	66	0.88	5.03	3.85	0.43	0
78	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	75	0.85	7.21	4.67	0.1	1
79	<i>MYBPC3</i>	Ben	VUS	chr11:47364677G>A	p.Gly416Ser	68	0.73	4.89	3.89	0.42	0
80	<i>MYBPC3</i>	Ben	Ben	chr11:47371333G>A	p.Ala216Thr	58	0.93	5.12	3.83	0.4	1
81	<i>MYBPC3</i>	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	57	1.4	5.4	3.8	0.41	2
82	<i>MYBPC3</i>	VUS	VUS	chr11:47364637C>T	p.Ala429Val	53	1.3	5.6	3.8	0.52	2
83	<i>MYBPC3</i>	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	43	1.2	4.3	2.7	0.3	1
84	<i>MYH7</i>	VUS	Path	chr14:23892910T>C	p.Met982Thr	51	0.9	5.4	3.6	0.3	1
84	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	51	0.9	5.4	3.6	0.3	1
85	<i>MYBPC3</i>	No call	VUS	chr11:47364393C>T	p.Ala482Val	44	1	5.2	3.9	0.37	2
86	<i>MYBPC3</i>	No call	VUS	chr11:47355201C>T	p.Arg1033Trp	50	0.8	5.2	3.7	0.52	1
87	<i>MYBPC3</i>	Ben	VUS	chr11:47355475C>G	p.Gln998Glu	51	1.4	4.2	3.7	0.57	2
88	<i>MYBPC3</i>	VUS	VUS	chr11:47364209A>G	p.Asn515Ser	57	0.92	4.62	3.21	0.44	0
89	<i>MYH7</i>	VUS	Ben	chr14:23885257G>A	p.Ala1637Thr	38	0.9	5.9	3.5	0.32	0
90	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	40	0.8	4.2	3.2	0.38	0
91	<i>TPM1</i>	No call	VUS	chr15:63356304G>A	p.Glu272Lys	48	0.81	5.03	2.82	0.27	0
92	<i>MYBPC3</i>	Ben	Ben	chr11:47371333G>A	p.Ala216Thr	55	1.1	4.2	3.1	0.29	0
93	<i>MYBPC3</i>	No call	VUS	chr11:47353755C>T	p.Arg1228Cys	76	1.2	3.9	2.5	0.41	1
94	<i>MYH7</i>	Ben	Ben	chr14:23886409C>G	p.Ser1491Cys	38	1	4.3	2.7	0.37	2
95	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	45	1.03	5.23	2.53	0.44	1
96	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	51	1.3	4.4	3	0.39	2
97	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	52	1.1	5.2	3.7	0.4	3
98	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	40	1.2	4.7	3.5	0.45	2
99	<i>MYBPC3</i>	No call	Ben	chr11:47372975C>A	p.Ala36Glu	51	0.96	5.18	3.62	0.24	0
100	<i>MYBPC3</i>	No call	VUS	chr11:47371591G>A	p.Arg160Gln	74	0.89	6.13	3.86	0.37	3
101	<i>MYL3</i>	No call	NA	chr3:46904845T>G	p.Asp12Glu	45	0.93	4.38	3.51	0.41	2
102	<i>MYBPC3</i>	VUS	VUS	chr11:47355553C>T	p.Arg972Trp	51	1	4.38	3.54	0.49	3
102	<i>MYH7</i>	Ben	Ben	chr14:23886409C>G	p.Ser1491Cys	51	1	4.38	3.54	0.49	3
103	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	45	0.92	5.07	3.19	0.4	1
104	<i>MYL2</i>	VUS	VUS	chr12:111353525G>T	p.Ala55Ser	53	0.87	5.1	2.89	0.49	2

105	<i>MYH7</i>	Ben	Ben	chr14:23886409C>G	p.Ser1491Cys	71	0.8	4.9	3.4	0.43	0
105	<i>MYBPC3</i>	Ben	Ben	chr11:47371333G>A	p.Ala216Thr	71	0.8	4.9	3.4	0.43	0
106	<i>MYBPC3</i>	No call	Ben	chr11:47355246G>C	p.Glu1018Gln	47	0.98	4.92	3.21	0.37	0
107	<i>MYBPC3</i>	No call	Ben	chr11:47371604C>G	p.Leu156Val	38	0.96	5.34	4.12	0.34	0
108	<i>MYBPC3</i>	No call	VUS	chr11:47355528G>A	p.Arg980His	54	0.8	4.76	3.09	0.33	0
109	<i>MYBPC3</i>	VUS	VUS	chr11:47364602G>A	p.Glu441Lys	48	1.08	5.06	4.04	0.42	2
110	<i>MYBPC3</i>	VUS	VUS	chr11:47364637C>T	p.Ala429Val	49	0.96	4.23	2.99	0.4	1
111	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	73	1.1	5.04	3.9	0.39	2
112	<i>MYBPC3</i>	No call	Ben	chr11:47371381A>G	p.Ser200Gly	52	NA	NA	NA	NA	2
113	<i>MYH7</i>	No call	Ben	chr14:23884982C>G	p.Ile1671Met	37	0.87	4.62	3.97	0.5	1
114	<i>MYBPC3</i>	Likely Path	VUS	chr11:47361266G>A	p.Arg668His	56	0.83	4.76	3.03	0.3	0
115	<i>MYBPC3</i>	VUS	VUS	chr11:47355234C>T	p.Arg1022Cys	59	0.94	4.83	3.71	0.38	3
116	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	70	NA	NA	3.35	NA	2
117	<i>MYBPC3</i>	Ben	Ben	chr11:47355192C>T	p.Arg1036Cys	72	0.77	5.08	3.62	0.51	3
118	<i>MYBPC3</i>	No call	VUS	chr11:47354392A>G	p.Lys1155Glu	50	0.87	4.75	2.67	0.36	0
119	<i>MYL3</i>	VUS	NA	chr3:46899903A>G	p.Glu177Gly	56	1.1	4.71	3.75	0.45	2
120	<i>MYH7</i>	Ben	Ben	chr14:23886409C>G	p.Ser1491Cys	42	0.86	4.96	3.63	0.48	1
121	<i>MYL3</i>	No call	NA	chr3:46904811G>A	p.Ala24Thr	52	0.78	4.3	3.13	0.38	0
122	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	42	1.13	5.45	4.1	0.3	1
123	<i>MYBPC3</i>	Ben	VUS	chr11:47364677G>A	p.Gly416Ser	69	1.05	4.93	3.66	0.35	2
124	<i>MYBPC3</i>	Ben	Ben	chr11:47355192C>T	p.Arg1036Cys	70	NA	NA	NA	NA	1
125	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	51	1.28	4.48	3.72	0.36	2
126	<i>MYBPC3</i>	Ben	Ben	chr11:47355192C>T	p.Arg1036Cys	49	0.95	4.36	3.66	0.44	1
126	<i>MYBPC3</i>	VUS	Ben	chr11:47371609T>C	p.Ile154Thr	49	0.95	4.36	3.66	0.44	1
127	<i>MYBPC3</i>	VUS	VUS	chr11:47364637C>T	p.Ala429Val	58	1.05	4.27	3.68	0.45	2
128	<i>MYBPC3</i>	No call	VUS	chr11:47353429C>T	p.Pro1273Leu	53	0.81	5.4	3.08	0.39	0
129	<i>MYBPC3</i>	No call	VUS	chr11:47364614G>A	p.Val437Met	43	0.78	4.34	3.04	0.3	0
130	<i>MYH7</i>	Ben	Ben	chr14:23886409C>G	p.Ser1491Cys	61	0.85	5.1	3.73	0.41	0
131	<i>MYL2</i>	VUS	Path	chr12:111348923G>C	p.Lys153Asn	81	0.94	4.72	3.02	0.57	1
132	<i>TNNT2</i>	VUS	Ben	chr1:201335991A>G	p.Met60Val	54	0.73	4.95	3.21	0.38	0
133	<i>MYBPC3</i>	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	56	0.9	5.34	4.03	0.4	0
134	<i>MYH7</i>	No call	Path	chr14:23896983C>T	p.Arg567Cys	47	0.68	4.31	2.89	0.4	1
135	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	63	0.96	4.73	2.97	0.46	1
136	<i>MYBPC3</i>	No call	VUS	chr11:47353755C>T	p.Arg1228Cys	43	1.15	4.75	3.24	0.44	0
137	<i>MYH7</i>	Likely Path	Path	chr14:23894051G>A	p.Arg869His	44	NA	NA	NA	NA	0
138	<i>MYH7</i>	No call	Path	chr14:23892845C>G	p.Gln1004Glu	52	0.78	4.36	3.56	0.39	1
139	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	62	0.78	4.73	3.56	0.39	0
140	<i>MYH7</i>	No call	Ben	chr14:23896928T>C	p.Ile585Thr	48	NA	NA	NA	NA	0
141	<i>MYBPC3</i>	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	55	0.97	4.93	3.67	0.3	0
142	<i>MYH7</i>	Likely Path	Path	chr14:23896955A>G	p.His576Arg	61	0.7	4.98	3.74	0.42	0
143	<i>MYBPC3</i>	Ben	Ben	chr11:47371333G>A	p.Ala216Thr	49	0.93	4.93	4.14	0.41	1
144	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	54	1.01	4.54	3.34	0.49	0
144	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	54	1.01	4.54	3.34	0.49	0
145	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	56	0.83	5.27	4.15	0.35	0
146	<i>MYBPC3</i>	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	53	1.05	4.86	2.89	0.33	0
147	<i>MYBPC3</i>	VUS	VUS	chr11:47356616C>T	p.Pro961Leu	42	NA	NA	NA	NA	1
148	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	51	0.9	5.13	3.58	0.46	1
149	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	57	0.95	4.65	3.25	0.45	0
150	<i>MYL2</i>	No call	No call	chr12:111356937G>T	p.Glu22*	56	1.13	5.3	4.28	0.31	0
151	<i>MYBPC3</i>	VUS	VUS	chr11:47356616C>T	p.Pro961Leu	53	0.9	4.93	3.6	0.28	0
151	<i>MYBPC3</i>	Ben	VUS	chr11:47364677G>A	p.Gly416Ser	53	0.9	4.93	3.6	0.28	0
152	<i>MYBPC3</i>	Ben	Ben	chr11:47355192C>T	p.Arg1036Cys	38	0.84	5.05	3.43	0.37	0
152	<i>MYH7</i>	VUS	Path	chr14:23885010G>A	p.Arg1662His	38	0.84	5.05	3.43	0.37	0
153	<i>MYBPC3</i>	Ben	VUS	chr11:47359047G>A	p.Ala833Thr	48	NA	NA	NA	NA	4
154	<i>MYBPC3</i>	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	52	1.13	5.37	4.84	0.32	2
155	<i>MYBPC3</i>	Ben	Ben	chr11:47355192C>T	p.Arg1036Cys	47	0.86	5.15	4.17	0.41	0
156	<i>MYBPC3</i>	Ben	Ben	chr11:47357479G>A	p.Val896Met	57	0.78	5	3.41	0.29	0
157	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	46	0.78	5.02	3.53	0.47	3
158	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	63	0.84	4.84	4.08	0.33	3
159	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	65	0.85	4.66	3.09	0.44	0
160	<i>MYH7</i>	VUS	VUS	chr14:23899810G>A	p.Val320Met	63	1.02	4.54	3.69	0.43	0

161	<i>TNNT2</i>	No call	VUS	chr1:201334778T>G	p.Val75Gly	36	0.79	4.96	3.45	0.43	0
162	<i>TPM1</i>	No call	Path	chr15:63349257G>A	p.Arg105His	46	1.3	4.87	3.9	0.35	1
163	<i>MYBPC3</i>	No call	VUS	chr11:47354440G>A	p.Val1139Ile	38	1.05	4.61	3.95	0.32	2
164	<i>MYH7</i>	No call	Path	chr14:23885422G>A	p.Glu1582Lys	40	0.7	5.48	3.35	0.35	1
165	<i>MYBPC3</i>	No call	Ben	chr11:47361206C>T	p.Thr688Met	50	1.36	4.83	3.68	0.51	0
166	<i>MYH7</i>	VUS	Ben	chr14:23884924G>A	p.Val1691Met	65	0.93	4.97	3.93	0.37	2
166	<i>MYBPC3</i>	Ben	VUS	chr11:47367871G>A	p.Arg326Gln	65	0.93	4.97	3.93	0.37	2
167	<i>MYH7</i>	No call	Path	chr14:23893251G>C	p.Glu929Asp	41	0.97	4.37	3.09	0.38	0
168	<i>MYH7</i>	Likely Path	Path	chr14:23894051G>A	p.Arg869His	41	0.83	4.67	3.08	0.39	0
169	<i>MYL3</i>	Likely Path	NA	chr3:46902303C>G	p.Ala57Gly	81	0.87	4.94	3.08	0.47	0
170	<i>MYBPC3</i>	Ben	Ben	chr11:47371333G>A	p.Ala216Thr	84	0.83	4.87	NA	0.37	3
171	<i>MYBPC3</i>	Ben	Ben	chr11:47371333G>A	p.Ala216Thr	46	1.14	4.69	3.23	0.41	1
172	<i>MYBPC3</i>	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	40	1.02	5.08	3.8	0.4	0
173	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	43	0.78	4.19	3.23	0.41	1
174	<i>MYH7</i>	No call	Path	chr14:23884344G>A	p.Gly1807Ser	39	0.74	4.48	3.06	0.45	0
175	<i>MYBPC3</i>	Ben	VUS	chr11:47367871G>A	p.Arg326Gln	50	0.74	5.27	3.38	0.39	0
176	<i>MYBPC3</i>	No call	VUS	chr11:47360203C>T	p.Arg726Cys	51	0.85	5.53	3.83	0.39	0
177	<i>MYBPC3</i>	VUS	VUS	chr11:47355553C>T	p.Arg972Trp	48	0.81	4.78	4.23	0.38	0
178	<i>MYBPC3</i>	VUS	VUS	chr11:47358987G>A	p.Gly853Ser	41	0.74	4.28	3.06	0.4	0
179	<i>MYBPC3</i>	No call	Ben	chr11:47361291G>T	p.Val660Leu	48	0.78	5.23	3.38	0.43	0
179	<i>TNNT2</i>	No call	VUS	chr1:201334327G>A	p.Asp125Asn	48	0.78	5.23	3.38	0.43	0
180	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	47	0.83	4.93	3.23	0.3	0
181	<i>MYBPC3</i>	No call	Ben	chr11:47369995A>T	p.Asn251Ile	38	0.65	4.5	2.53	0.34	0
182	<i>MYBPC3</i>	No call	VUS	chr11:47359010G>A	p.Arg845His	58	0.86	5.47	3.73	0.35	2
183	<i>MYBPC3</i>	Ben	VUS	chr11:47367871G>A	p.Arg326Gln	70	0.89	5.29	3.72	0.4	0
184	<i>MYBPC3</i>	No call	VUS	chr11:47367892A>T	p.Glu319Val	53	0.74	4.93	2.94	0.38	2
185	<i>MYBPC3</i>	VUS	VUS	chr11:47364637C>T	p.Ala429Val	76	0.73	5.04	4.07	0.34	1
186	<i>MYBPC3</i>	VUS	VUS	chr11:47355553C>T	p.Arg972Trp	39	1	5.23	4.33	0.32	1
187	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	66	1.23	4.55	4.36	0.46	1
188	<i>MYH7</i>	VUS	Path	chr14:23892910T>C	p.Met982Thr	53	1.14	5.08	3.26	0.41	4
189	<i>MYH7</i>	No call	Path	chr14:23891497T>G	p.Met1046Arg	71	0.89	3.85	3.29	0.42	1
190	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	44	0.84	4.87	3.56	0.41	0
191	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	37	0.96	5.28	4.23	0.36	3
192	<i>MYBPC3</i>	No call	Ben	chr11:47354857G>A	p.Arg1073Gln	59	0.78	4.93	3.48	0.33	1
193	<i>MYBPC3</i>	No call	VUS	chr11:47354440G>A	p.Val1139Ile	49	1.28	3.96	3.89	0.37	2
194	<i>TNNI3</i>	No call	VUS	chr19:55666173G>A	p.Arg103His	51	1.35	4.15	3.38	0.35	0
195	<i>MYBPC3</i>	VUS	Ben	chr11:47362731G>A	p.Glu619Lys	59	1.04	5.57	3.89	0.38	1
196	<i>MYBPC3</i>	VUS	VUS	chr11:47355553C>T	p.Arg972Trp	37	1.35	4.2	4.16	0.27	0
197	<i>MYBPC3</i>	Ben	Ben	chr11:47354209G>A	p.Glu1179Lys	40	1.13	4.88	4.08	0.41	3
198	<i>MYH7</i>	VUS	Path	chr14:23887443G>A	p.Arg1382Gln	45	0.98	5.14	4.2	0.4	5
199	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	76	0.87	5.08	3.78	0.34	3
200	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	71	0.96	4.57	3.56	0.32	2
200	<i>MYBPC3</i>	Ben	VUS	chr11:47363699C>A	p.Leu545Met	71	0.96	4.57	3.56	0.32	2
201	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	64	0.9	5.36	4.23	0.47	1
202	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	71	0.89	4.68	3.67	0.46	1
203	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	50	0.95	5	3.69	0.39	1
204	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	69	1	4.89	3.85	0.41	1
205	<i>MYBPC3</i>	No call	Ben	chr11:47361206C>T	p.Thr688Met	81	1.05	4.89	3.56	0.29	2
206	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	45	0.73	4.72	3.79	0.44	0
207	<i>TPM1</i>	VUS	VUS	chr15:63356319G>A	p.Ala277Thr	37	0.83	5.17	3.05	0.31	0
208	<i>MYH7</i>	No call	Ben	chr14:23902788G>A	p.Val52Met	45	0.74	5.06	3.46	0.34	2
209	<i>MYH7</i>	Ben	Ben	chr14:23886409C>G	p.Ser1491Cys	56	1.2	4.37	2.85	0.47	0
210	<i>MYBPC3</i>	VUS	VUS	chr11:47364637C>T	p.Ala429Val	54	0.82	4.25	3.08	0.4	0
211	<i>TNNT2</i>	Likely Path	Path	chr1:201328373C>T	p.Arg278Cys	79	1.09	4.68	3.74	0.39	0
211	<i>MYBPC3</i>	Path	VUS	chr11:47364249C>T	p.Arg502Trp	79	1.09	4.68	3.74	0.39	0
212	<i>MYBPC3</i>	No call	VUS	chr11:47353755C>T	p.Arg1228Cys	53	0.78	4.22	3.01	0.42	0
213	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	60	0.68	7.83	4.03	0.11	0
214	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	48	0.86	4.98	4.29	0.37	0
215	<i>MYBPC3</i>	No call	Ben	chr11:47361213G>C	p.Ala686Pro	57	0.84	4.48	3.68	0.44	3
216	<i>MYH7</i>	VUS	Ben	chr14:23885257G>A	p.Ala1637Thr	57	0.98	4.77	3.63	0.45	3
217	<i>MYBPC3</i>	Ben	Ben	chr11:47371333G>A	p.Ala216Thr	52	0.7	4.93	3.54	0.35	0

218	<i>MYBPC3</i>	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	46	0.74	4.63	3.38	0.38	1
219	<i>MYBPC3</i>	No call	Ben	chr11:47372895C>T	p.Arg63Trp	50	0.7	5.08	3.86	0.38	0
220	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	46	0.72	4.68	3.39	0.37	2
221	<i>MYH7</i>	VUS	Ben	chr14:23885257G>A	p.Ala1637Thr	45	1.08	4.95	3.99	0.34	1
222	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	59	1.19	5.63	4.46	0.43	1
223	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	48	1.12	4.61	3.8	0.47	3
224	<i>MYL3</i>	No call	NA	chr3:46902471T>C	p.Phe46Leu	53	0.72	4.68	3.05	0.35	0
225	<i>MYBPC3</i>	No call	VUS	chr11:47353755C>T	p.Arg1228Cys	40	0.81	5.19	3.55	0.37	2
226	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	54	0.86	4.89	3.99	0.41	0
227	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	67	0.95	4.75	3.78	0.33	1
228	<i>MYH7</i>	No call	Ben	chr14:23888736T>C	p.Val1270Ala	55	0.83	4.69	3.08	0.36	0
229	<i>MYBPC3</i>	Ben	Ben	chr11:47355192C>T	p.Arg1036Cys	48	0.7	4.15	2.85	0.39	1
230	<i>MYL2</i>	No call	VUS	chr12:111348913C>T	p.His157Tyr	42	0.84	4.08	3.56	0.43	1
231	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	61	0.98	5.13	5.29	0.34	0
232	<i>MYBPC3</i>	No call	VUS	chr11:47354403C>T	p.Ala1151Val	54	0.83	4.28	3.3	0.39	2
233	<i>MYBPC3</i>	Ben	VUS	chr11:47355294C>T	p.Arg1002Trp	39	0.98	5.39	3.82	0.32	2
234	<i>TNNI3</i>	No call	VUS	chr19:55666173G>A	p.Arg103His	51	0.96	4.58	3.94	0.38	0
235	<i>MYBPC3</i>	No call	VUS	chr11:47355528G>A	p.Arg980His	44	0.92	4.93	3.98	0.34	2
236	<i>MYBPC3</i>	Ben	VUS	chr11:47367871G>A	p.Arg326Gln	75	0.96	4.36	3.23	0.33	1
237	<i>MYBPC3</i>	Ben	Ben	chr11:47355192C>T	p.Arg1036Cys	61	0.98	4.5	3.78	0.36	0
238	<i>MYL3</i>	Likely Path	NA	chr3:46900980G>A	p.Val156Met	44	0.94	4.65	3.74	0.34	3
239	<i>TNNT2</i>	No call	Path	chr1:201342373A>C	p.Ile4Leu	41	0.94	5.3	3.68	0.4	3
240	<i>MYBPC3</i>	VUS	VUS	chr11:47355553C>T	p.Arg972Trp	40	0.85	4.63	3.45	0.37	0
241	<i>MYBPC3</i>	Ben	VUS	chr11:47355475C>G	p.Gln998Glu	49	0.9	4.32	3.43	0.36	1
242	<i>MYBPC3</i>	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	49	0.89	4.75	3.46	0.39	2
243	<i>MYBPC3</i>	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	68	1.26	4.85	4.04	0.26	1
243	<i>MYBPC3</i>	Ben	VUS	chr11:47364234G>A	p.Gly507Arg	68	1.26	4.85	4.04	0.26	1
244	<i>MYBPC3</i>	VUS	Ben	chr11:47364189G>A	p.Ala522Thr	42	0.89	4.25	3.57	0.42	1

ID, participants with sarcomere variants were numbered consecutively. LMM, variant call using the Laboratory for Molecular Medicine database. ppHCM, variant call using the polyphen HCM algorithm. Prot, protein change. LVWT, left ventricular wall thickness (cm). LVDD, left ventricular diastolic diameter (cm). LAD, left atrial diameter (cm). FS, Fractional shortening. NA indicates that the data was not available for our analysis. N Phys. Risk Factors, the number of physiologic risk factors an individual has including hyperlipidemia, hypertension, obesity and diabetes.

Table S4 Number of individuals with at least one variant as evaluated by two approaches

Framingham Heart Study Offspring Cohort									
	Pathogenic ^a		Benign		VUS		No Call ^b		Total
	LMM	ppHCM	LMM	ppHCM	LMM	ppHCM	LMM	ppHCM	
<i>MYBPC3</i>	4	1	33	45	37	44	18	2	92
<i>MYH7</i>	2	21	0	6	13	7	21	2	36
<i>MYL3</i>	2	0	0	0	7	12	3	0	12
<i>MYL2</i>	4	5	0	0	2	2	1	0	7
<i>TNNT2</i>	1	1	2	0	2	4	1	1	6
<i>ACTC1</i>	0	2	0	0	0	1	3	0	3
<i>TNNI3</i>	1	0	0	0	0	1	1	1	2
<i>TPM1</i>	0	0	0	0	0	2	2	0	2
Total	14	30	35	51	61	73	50	6	158

Jackson Heart Study Cohort									
	Pathogenic ^a		Benign		VUS		No Call ^b		Total
	LMM	ppHCM	LMM	ppHCM	LMM	ppHCM	LMM	ppHCM	
<i>MYBPC3</i>	2	1	94	63	51	126	45	0	186
<i>MYH7</i>	3	17	12	22	13	2	14	1	42
<i>MYL3</i>	2	0	0	0	1	0	5	1	8
<i>TNNT2</i>	0	1	0	0	2	2	2	1	4
<i>MYL2</i>	2	4	0	1	1	2	4	0	7
<i>TPM1</i>	0	3	0	0	1	3	5	0	6
<i>TNNI3</i>	0	0	0	0	0	2	2	0	2
<i>ACTC1</i>	0	0	0	0	0	0	0	0	0
Total	8	26	105	85	69	137	75	3	244

LMM, the CLIA certified Partner’s Laboratory for Molecular Medicine database; ppHCM, the PolyPhen HCM algorithm; VUS, Variant of unknown significance.

^aLMM pathogenic and likely pathogenic categories are grouped together here under the “Pathogenic” category. ^bVariants classified as “No Call” under LMM represent variants not seen by the LMM and therefore not in the LMM’s database. Polyphen HCM limits its calls to missense variants so all nonsense, indel and splice variants are listed as “No Call”.

Table S5 Stratified summary of unscaled echocardiography measurements

Parameter	Framingham Heart Study							Jackson Heart Study						
	N ^b	Age	Female	LVWT ^c	LVDD ^c	LAD ^c	FS ^c	N ^b	Age	Female	LVWT ^c	LVDD ^c	LAD ^c	FS ^c
No Risk Factors^a	855	58.3 (9.2)	63%	9.6 (1.2)	47.4 (4.9)	38.4 (5.0)	0.37 (.06)	972	55.5 (12.7)	58%	9.2 (1.9)	48.2 (4.8)	34.7 (4.5)	0.39 (.073)
≥1 Sarcomere Variant	158	59.7 (9.4)	43%	10.1*** (1.3)	48.3* (4.9)	40.1*** (5.0)	0.36 (.05)	244	57.9 (11.8)	62%	9.5 (1.6)	48.5 (4.9)	35.6** (4.5)	0.39 (.068)
MYBPC3	92	59.3	46%	10.0*	48.6*	40.4***	0.36*	186	58.6	61%	9.5*	48.8	36.0***	0.39
MYH7	36	59.4	39%	10.0	48.6	40.4*	0.36	42	57.2	79%	8.9	48.1	34.8	0.40
MYL3	12	61.8	42%	10.4	46.7	39.1	0.40	8	56.3	57%	9.5	46.3	34.0	0.39
MYL2	7	61.7	50%	10.2	47.5	38.8	0.38	4	58.7	100%	9.5	48.0	34.4	0.45
TNNT2	6	57.0	50%	10.8	47.1	39.9	0.35	7	51.8	25%	8.8	49.1	34.6	0.40
TPMI	3	65.7	0%	10.2	49.9	36.3	0.37	6	55.0	40%	10.7	50.3**	33.5	0.30 **
ACTC1	2	57.0	50%	1.11	43.3	38.0	0.41	0						
TNNI3	2	61.5	50%	10.0	48.0	39.4	0.38	2			11.6	43.7	36.6	0.36
LMM (Likely) Pathogenic	14	63.0 (10.5)	38%	10.6* (1.1)	48.2 (5.0)	39.9 (4.2)	0.34 (.07)	8	54.0 (14.1)	50%	8.9 (1.2)	47.5 (1.5)	34.7 (3.9)	0.40 (.069)
PolyPhen HCM Pathogenic	30	61.4 (9.2)	42%	10.5* (1.6)	47.8 (5.8)	38.9 (5.1)	0.37 (.06)	26	59.0 (13.3)	59%	9.1 (1.6)	48.3 (4.3)	34.6 (4.2)	0.38 (.071)
LMM Benign	35	59.2 (9.4)	32%	10.1 (1.6)	48.8 (5.0)	41.6*** (4.5)	0.37 (.05)	105	59.5 (11.9)	64%	9.4 (1.5)	49.0 (5.5)	36.2** (4.5)	0.39 (.078)
PolyPhen HCM Benign	51	59.7 (9.4)	47%	0.99 (1.2)	48.2 (4.6)	40.6** (4.9)	0.37 (.05)	85	59.3 (11.6)	66%	9.5 (1.7)	48.5 (3.8)	35.4 (4.2)	0.39 (.062)
≥2 Physiologic Risk Factors^a	575	62.1 (9.1)	35%	10.3*** (1.3)	49.3*** (5.2)	41.8*** (5.5)	0.35 *** (.07)	777	58.7 (11.0)	64%	9.8*** (1.6)	49.0*** (4.7)	35.9*** (4.8)	0.39 (.076)
≥1 Sarcomere Variant + ≥2 Physiologic Risk Factors^a	62	61.3 (10.2)	32%	10.4*** (1.2)	49.6*** (4.4)	42.1*** (4.6)	0.37 (.05)	97	59.5 (11.1)	64%	10.0*** (1.6)	48.7 (4.5)	36.5*** (4.0)	0.40 (.063)

^aPhysiologic risk factors include hyperlipidemia, hypertension, obesity and diabetes. Standard deviations for this group are listed parenthetically. ^bN is number of individuals. ^cMeasurements (in mm) of LVWT, left ventricular wall thickness; LVDD, left ventricular diastolic diameter; LAD, left atrial diameter. Significance is denoted: *p<.05; **p<.01; ***p<.001

Table S6. Low frequency (0.5-1%) or common variants (1-10%) identified in either FHS or JHS population

rsID	Gene	Coding Coordinate	Protein	FHS MAF	JHS MAF
rs3730238	<i>TNNT2</i>	chr1:201330429A>G	p.Lys247Arg	1.76%	0.00%
rs3729823	<i>MYH7</i>	chr14:23886409C>G	p.Ser1491Cys	1.45%	0.31%
rs3729799	<i>MYBPC3</i>	chr11:47355294G>A	p.Arg1002Trp	0.06%	0.77%
rs3729952	<i>MYBPC3</i>	chr11:47359046C>T	p.Ala833Val	0.00%	2.27%
rs35736435	<i>MYBPC3</i>	chr11:47364234G>A	p.Gly507Arg	0.00%	0.72%
rs11570076	<i>MYBPC3</i>	chr11:47365122C>T	p.Arg382Trp	0.00%	4.29%
	<i>MYBPC3</i>	chr11:47369220G>A	p.Gly227Glu	0.00%	1.43%
rs3729989	<i>MYBPC3</i>	chr11:47370041A>G	p.Ser236Gly	0.00%	5.51%
	<i>MYBPC3</i>	chr11:47371449G>A	p.Arg176His	0.00%	1.46%
rs3729986	<i>MYBPC3</i>	chr11:47371598G>A	p.Val158Met	0.00%	2.02%
rs77615401	<i>TNNI3</i>	chr19:55667607C>T	p.Pro82Ser	0.00%	2.09%

Table S7. Number of individuals at risk in Kaplan-Meier analyses

Age	35	40	45	50	55	60	65
No Risk Factors	782	782	778	751	685	524	362
Genetic Risk	99	99	98	96	84	67	39
Physiologic Risk	495	490	482	450	418	359	251
Gen. + Physio. Risk	59	59	58	51	48	38	26

Table S8. Distribution of first cardiovascular disease events observed in Kaplan-Meier analyses

	MI	AP	CI	CVA	IC	CHF	Total
None	10	18	2	10	6	2	48
Genetic	6	5	0	0	2	1	14
Physiologic	33	48	0	14	13	2	110
Gen. + Phys.	2	3	1	0	2	1	9

MI, myocardial infarction. AP, angina pectoris. CI, coronary insufficiency. CVA, cerebrovascular accident. IC, intermittent claudication. CHF, congestive heart failure.