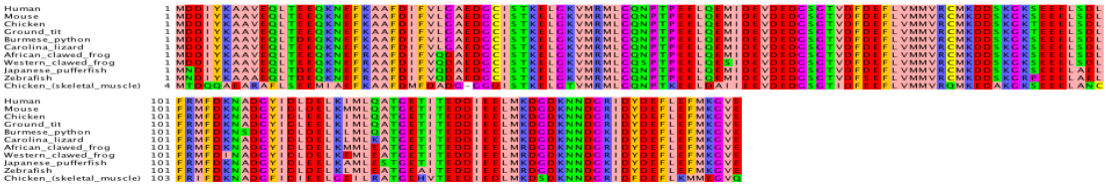
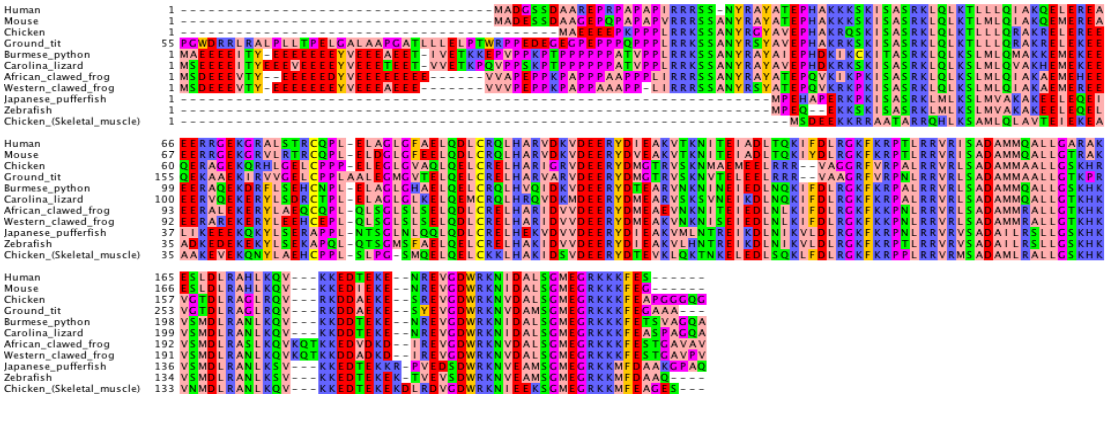
Supplementary Fig. 1 | Multiple sequence alignments of thin filament proteins. Proteins are for cardiac isoforms, unless indicated otherwise. Sequences were aligned using MUSCLE, followed by manual refinement in JalView2. **a**, TnC; **b**, TnI and **c**, TnT. Residues: acidic (red); basic (blue); polar (green); aromatic (orange); aliphatic (pink); cysteine (yellow); and proline and glycine (magenta)

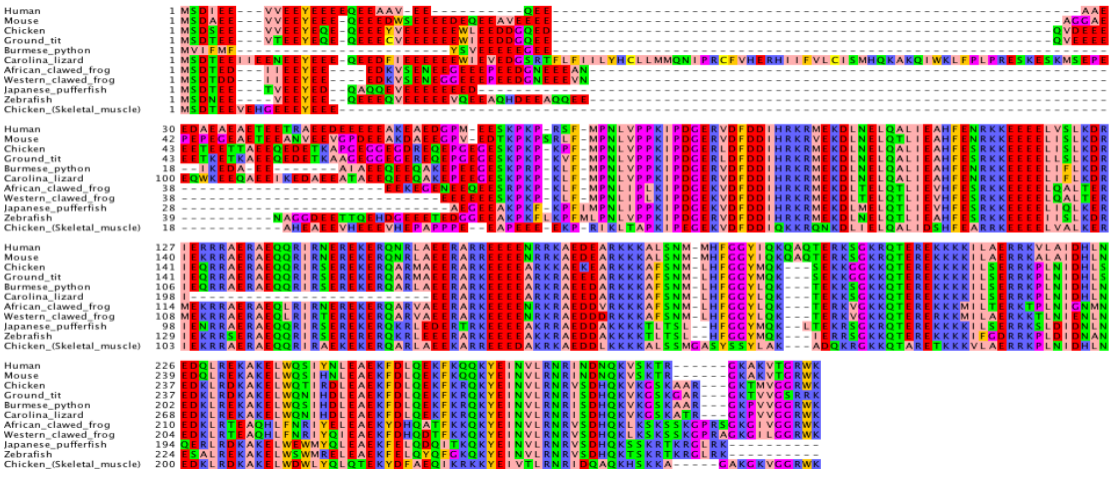
a



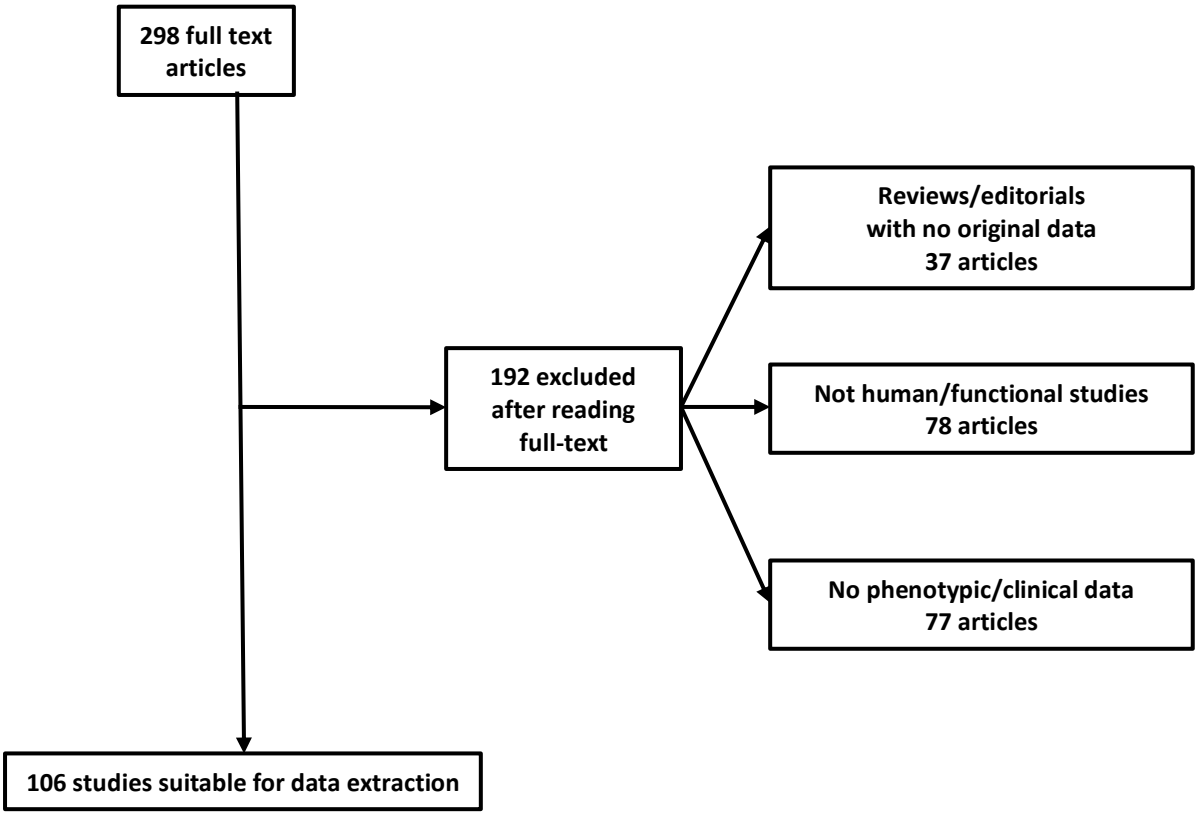
b



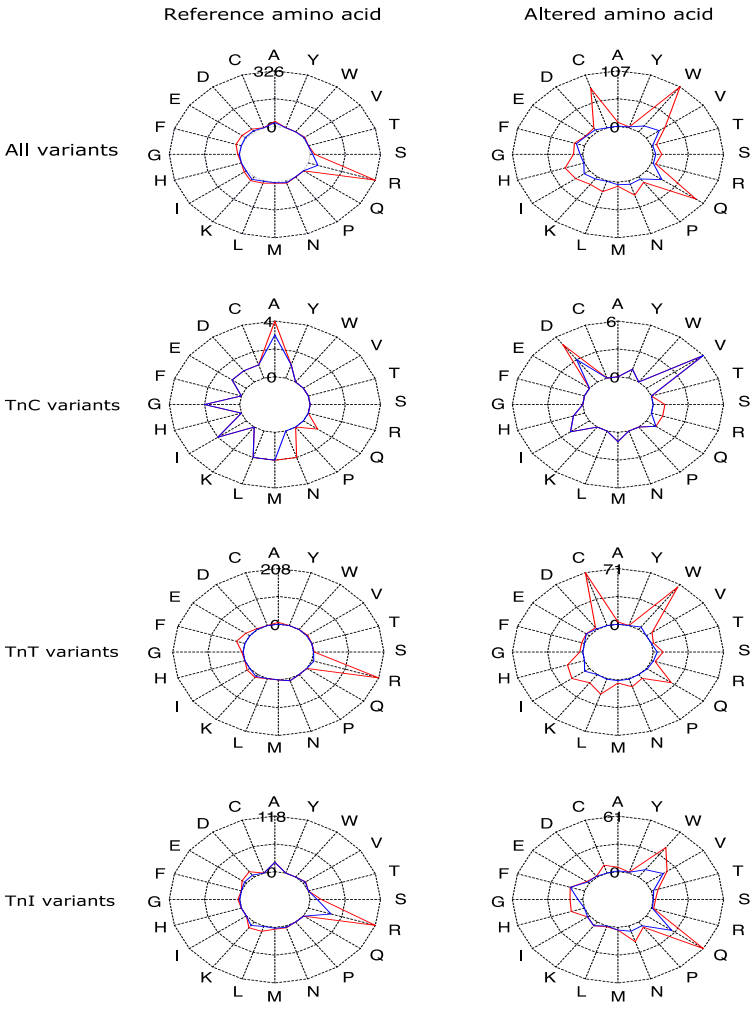
c



Supplementary Fig. 2 | Flow chart of total number of studies used for meta-analysis of troponin variations in cardiomyopathies.



Supplementary Fig.3 | Spider plot for the distributions of reference and altered amino acids among variants in troponins. The red line indicates total number of cases, and the blue line indicates cases carrying variants at known protein structural regions.



Supplementary Table 1. Inter-molecular interactions observed between residues in structures of troponin complexes, and the pathology of associated hotspots. Individual interactions are shown in Fig. 1.

Protein	Region	Both Ca^{2+} states	Ca^{2+}-saturated	Ca^{2+}-free	Tm	Actin	Ca^{2+} cation	Hot spot
TnT	1-89							
	90-129				+			HCM
	130-179							DCM
	200-240		+	+				
	241-290	+	+				+	HCM
TnC	1-100		+	+		+	+	
	101-160	+					+	
TnI	1-130	+	+	+				
	131-175		+	+		+		HCM
	176-210							DCM

Supplementary Table 2: List of mutations and references of all the articles finally included in the systematic review.

	PROTEIN LEVEL	CHROMOSOMIC LEVEL	PAT.	Index (families)	Affected	RS	G.D.	SIFT	Polyphen-2	Mutation Taster	References
TNNI3	NP_000354.4:p.Arg13Cys	NC_000019.9:g.55668489G>A	L.P.	2	2		180	Damaging	Benign		1
TNNI3	NP_000354.4:p.Arg21Cys	NC_000019.9:g.55668465G>A	L.P.	3	4	rs267607128	180	Damaging	Probably damaging	Disease causing	2, 3
TNNI3	NP_000354.4:p.Lys36Gln	NC_000019.9:g.55668420T>G	P.	3	5	rs267607130	53	Tolerated	Possibly damaging	Disease causing	4, 5
TNNI3	NP_000354.4:p.Arg74Pro	NC_000019.9:g.55667630C>G	L. P.	1	1	rs886039022	103	Damaging	Probably damaging	Disease causing	6
TNNI3	NP_000354.4:p.Leu100Phe	NC_000019.9:g.55666183G>A	L.P.	1	2	rs773216333	22	Damaging	Probably damaging	Disease causing	7
TNNI3	NP_000354.4:p.Glu124Gln	NC_000019.9:g.55666111C>G	LP.	2	8	rs727503506	29	Damaging	Probably damaging	Disease causing	8, 9
TNNI3	NP_000354.4:p.Asp127Tyr	NC_000019.9:g.55665568C>A	LP	1	1	rs1114167340	160	Damaging	Probably damaging	Disease causing	10
TNNI3	NP_000354.4:p.Gln130Arg	NC_000019.9:g.55665558T>C	LP.	1	1	rs1390435424	43	Tolerated	Benign	Polymorphism	11
TNNI3	NP_000354.4:p.Arg136Gln	NC_000019.9:g.55665540C>T	L.P.	1	1	rs730881069	43	Tolerated	Probably damaging	Disease causing	12, 13
TNNI3	NP_000354.4:p.Arg141Gln	NC_000019.9:g.55665525C>T	P.	16	17	rs397516347	43	Damaging	Probably damaging	Polymorphism	1, 14, 15, 16, 17, 18, 19, 20, 21, 22
TNNI3	NP_000354.4:p.Leu144Gln	NC_000019.9:g.55665516A>T	P.	4	31	rs121917760	113	Damaging	Probably damaging	Disease causing	23, 24
TNNI3	NP_000354.4:p.Leu144Pro	NC_000019.9:g.55665516A>G	L.P.	1	1	rs121917760	98	Damaging	Probably damaging	Disease causing	117
TNNI3	NP_000354.4:p.Leu144His	NC_000019.9:g.55665515_55665516delCAinsAT	L.P.	1	3						116
TNNI3	NP_000354.4:p.Arg145Gly	NC_000019.9:g.55665514G>C	P.	3	11	rs104894724	125	Damaging	Probably damaging	Disease causing	25, 26, 27
TNNI3	NP_000354.4:p.Arg145Trp	NC_000019.9:g.55665514G>A	P.	30	49	rs104894724	101	Damaging	Probably damaging	Disease causing	7, 13, 17, 18, 21, 23, 28, 29, 30, 31
TNNI3	NP_000354.4:p.Arg145Gln	NC_000019.9:g.55665513C>T	P.	9	12	rs397516349	43	Damaging	Probably damaging	Disease causing	7, 17, 18, 21, 26, 32
TNNI3	NP_000354.4:p.Val147Leu	NC_000019.9:g.55665508C>G	LP.	1	1	rs777782551	32	Damaging	Probably damaging		3
TNNI3	NP_000354.4:p.Ser150Cys	NC_000019.9:g.55665498G>C	L.P.	1	1		112	Damaging	Probably damaging	Disease causing	13
TNNI3	NP_000354.4:p.Met154Ile	NC_000019.9:g.55665485C>T	L.P.	2	2	rs397516350	10	Damaging	Benign	Disease causing	16
TNNI3	NP_000354.4:p.Ala157Val	NC_000019.9:g.55665477G>A	P.	18	23	rs397516353	64	Damaging	Possibly damaging	Disease causing	16, 17, 18, 19, 21, 33
TNNI3	NP_000354.4:p.Ala161Asp	NC_000019.9:g.55665465G>T	LP.	1	1		126	Damaging	Benign	Disease causing	34
TNNI3	NP_000354.4:p.Arg162Trp	NC_000019.9:g.55665463G>A	P.	8	8	rs368861241	101	Damaging	Probably damaging	Disease causing	16, 26, 29, 35, 36
TNNI3	NP_000354.4:p.Arg162Gln	NC_000019.9:g.55665462C>T	P.	14	24	rs397516354	43	Tolerated	Possibly damaging	Disease causing	15, 17, 18, 20, 36, 37, 38
TNNI3	NP_000354.4:p.Arg162Pro	NC_000019.9:g.55665462C>G	P.	4	6	rs397516354	103	Damaging	Possibly damaging	Disease causing	19, 22, 37
TNNI3	NP_000354.4:p.Lys164Thr	NC_000019.9:g.55665456T>G	L.P.	1	1	rs546367368	78	Tolerated	Probably damaging	Disease causing	21
TNNI3	NP_000354.4:p.Ser166Phe	NC_000019.9:g.55665450G>A	P.	12	16	rs727504242	155	Damaging	Possibly damaging	Disease causing	17, 18, 20, 21, 29, 39, 40, 41
TNNI3	NP_000354.4:p.Arg170Trp	NC_000019.9:g.55665439G>A	L.P.	2	2	rs727503504	101	Damaging	Probably damaging	Disease causing	7, 13
TNNI3	NP_000354.4:p.Arg170Gln	NC_000019.9:g.55665438C>T	L.P.	2	2	rs727503503	43	Damaging	Probably damaging	Disease causing	42

	PROTEIN LEVEL	CHROMOSOMIC LEVEL	PAT.	Index (families)	Affected	RS	G.D.	SIFT	Polyphen-2	Mutation Taster	References
TNNI3	NP_000354.4:p.Ala171Thr	NC_000019.9:g.55665436C>T	L.P.	1	1	rs121917761	58	Tolerated	Probably damaging	Disease causing	23
TNNI3	NP_000354.4:p.Val176Met	NC_000019.9:g.55665421C>T	LP.	3	3	rs727503501	21	Damaging	Probably damaging		2, 22
TNNI3	NP_000354.4:p.Lys178Glu	NC_000019.9:g.55665415T>C	L.P.	1	1	rs104894730	56	Damaging	Probably damaging	Disease causing	14, 23
TNNI3	NP_000354.4:p.Asp180Gly	NC_000019.9:g.55665408T>C	L.P.	4	7		94	Tolerated	Probably damaging	Disease causing	5, 21, 43
TNNI3	NP_000354.4:p.Glu182Lys	NC_000019.9:g.55665403C>T	L.P.	1	1	rs397516355	56	Tolerated	Benign	Disease causing	2
TNNI3	NP_000354.4:p.Lys183Glu	NC_000019.9:g.55665400T>C	P.	1	3	rs730881077	56	Tolerated	Benign	Disease causing	17, 18
TNNI3	NP_000354.4:p.Lys183Asn	NC_000019.9:g.55665398C>A	P.	6	6		94	Damaging	Possibly damaging	Disease causing	12, 13, 21
TNNI3	NP_000354.4:p.Glu184Lys	NC_000019.9:g.55663285C>T	L.P.	1	1	rs397516356	56	Tolerated	Benign	Disease causing	44
TNNI3	NP_000354.4:p.Asn185Lys	NC_000019.9:g.55663280G>T	L.P.	3	4	rs267607129	94	Tolerated	Benign	Polymorphism	4, 21, 45
TNNI3	NP_000354.4:p.Arg186Gln	NC_000019.9:g.55663278C>T	P.	9	26	rs397516357	43	Tolerated	Possibly damaging	Disease causing	13, 17, 18, 19, 22, 46, 47
TNII3	NP_000354.4:p.Val188Ala	NC_000019.9:g.55663272A>G	LP.	1	2		64	Tolerated	Probably damaging		49
TNNI3	NP_000354.4:p.Gly189Glu	NC_000019.9:g.55663269C>T	L. P.	1	1	rs587782980	98	Tolerated	Probably damaging	Disease causing	3
TNNI3	NP_000354.4:p.Asp190Gly	NC_000019.9:g.55663266T>C	L.P.	2	14	rs104894728	94	Damaging	Probably damaging	Disease causing	23, 28
TNNI3	NP_000354.4:p.Arg192Cys	NC_000019.9:g.55663261G>A	L.P.	2	2	rs727503499	180	Damaging	Probably damaging	Disease causing	13, 21
TNNI3	NP_000354.4:p.Arg192His	NC_000019.9:g.55663260C>T	P.	5	5	rs104894729	29	Damaging	Probably damaging	Disease causing	23, 50, 51, 52
TNNI3	NP_000354.4:p.Asn194Ser	NC_000019.9:g.55663254T>C	LP.	1	1	rs730881081	46	Damaging	Probably damaging	Disease causing	22
TNNI3	NP_000354.4:p.Asp196Asn	NC_000019.9:g.55663249C>T	P.	7	9	rs104894727	23	Damaging	Probably damaging	Disease causing	3, 17, 18, 19, 22
TNNI3	NP_000354.4:p.Leu198Val	NC_000019.9:g.55663243G>C	L.P.	4	5	rs727504285	32	Tolerated	Possibly damaging	Disease causing	222, 53
TNNI3	NP_000354.4:p.Leu198Pro	NC_000019.9:g.55663242A>G	L.P.	1	1		98	Tolerated	Probably damaging	Disease causing	37
TNNI3	NP_000354.4:p.Ser199Gly	NC_000019.9:g.55663240T>C	L.P.	1	1		56	Damaging	Probably damaging	Disease causing	17, 18
TNNI3	NP_000354.4:p.Ser199Asn	NC_000019.9:g.55663239C>T	P.	5	12	rs730881091	46	Damaging	Probably damaging	Disease causing	17, 18, 30
TNNI3	NP_000354.4:p.Met201Thr	NC_000019.9:g.55663233A>G	L.P.	2	2	rs727504365	81	Damaging	Probably damaging	Disease causing	21
TNNI3	NP_000354.4:p.Glu202Gly	NC_000019.9:g.55663230T>C	L.P.	1	1		98	Tolerated	Probably damaging	Disease causing	17, 18
TNNI3	NP_000354.4:p.Gly203Ser	NC_000019.9:g.55663228C>T	L.P.	1	3	rs267607127	56	Damaging	Probably damaging	Disease causing	26
TNNI3	NP_000354.4:p.Gly203Arg	NC_000019.9:g.55663228C>G	L.P.	1	2	rs267607127	125	Damaging	Probably damaging	Disease causing	17, 18
TNNI3	NP_000354.4:p.Arg204Cys	NC_000019.9:g.55663225G>A	L. P.	1	1	rs727504243	180	Damaging	Probably damaging	Disease causing	115
TNNI3	NP_000354.4:p.Arg204His	NC_000019.9:g.55663224C>T	P.	6	7	rs727504275	29	Damaging	Probably damaging	Disease causing	37, 54, 55
TNNI3	NP_000354.4:p.Lys206Gln	NC_000019.9:g.55663219T>G	L.P.	1	1	rs104894725	53	Damaging	Probably damaging	Disease causing	26
TNNI3	NP_000354.4:p.Lys207Thr	NC_000019.9:g.55663215T>G	L.P.	2	4	rs3676722	78	Damaging	Possibly damaging	Disease causing	56
TNNI3	NP_000354.4:p.Glu209Ala	NC_000019.9:g.55663209T>G	L.P.	4	4	rs730881083	107	Damaging	Probably damaging	Disease causing	21

	PROTEIN LEVEL	CHROMOSOMIC LEVEL	PAT.	Index (families)	Affected	RS	G.D.	SIFT	Polyphen-2	Mutation Taster	References
TNNC1	NP_003271.1:p.Asp3Val	NC_000003.11:g.52488024T>A	L.P.	1	1	rs730881063	152	Damaging	Probably damaging	Disease causing	113
TNNC1	NP_003271.1:p.Tyr5His	NC_000003.11:g.52488019A>G	L.P.	1	1		83	Tolerated	Possibly damaging	Disease causing	5, 43, 57
TNNC1	NP_003271.1:p.Ala8Val	NC_000003.11:g.52488009G>A	L.P.	3	4	rs267607125	64	Tolerated	Possibly damaging	Disease causing	58
TNNC1	NP_003271.1:p.Leu29Gln	NC_000003.11:g.52486238A>T	L.P.	1	1	rs267607123	113	Tolerated	Benign	Disease causing	59
TNNC1	NP_003271.1:p.Ala31Ser	NC_000003.11:g.52486233C>A	L.P.	1	1	rs397514616	99	Damaging	Probably damaging	Disease causing	60
TNNC1	NP_003271.1:p.Leu41Met	NC_000003.11:g.52486203G>T	L. P.	1	1		15	Damaging	Probably damaging	Disease causing	114
TNNC1	NP_003271.1:p.Gln50Arg	NC_000003.11:g.52486175T>C	P.	1	4		43	Damaging	Possibly damaging	Disease causing	5, 61
TNNC1	NP_003271.1:p.Cys84Tyr	NC_000003.11:g.52485826C>T	L.P.	1	1	rs267607126	194	Damaging	Probably damaging	Disease causing	58
TNNC1	NP_003271.1:p.Met103Ile	NC_000003.11:g.52485768C>G	L.P.	2	5		10	Tolerated	Benign	Disease causing	43, 57
TNNC1	NP_003271.1:p.Glu134Asp	NC_000003.11:g.52485459C>A	L.P.	1	1	rs397516847	45	Tolerated	Possibly damaging	Disease causing	58
TNNC1	NP_003271.1:p.Asn144Asp	NC_000003.11:g.52485431T>C	L. P.	2	5	rs730881061	23	Damaging	Benign	Disease causing	7, 112
TNNC1	NP_003271.1:p.Ile148Val	NC_000003.11:g.52485419T>C	L.P.	2	2	rs397516848	29	Tolerated	Benign	Disease causing	43, 57, 63
TNNC1	NP_003271.1:p.Gly159Asp	NC_000003.11:g.52485301C>T	P.	2	9	rs104893823	94	Damaging	Probably damaging	Disease causing	5, 29, 64
TNNT2	NP_001001430.1:p.Lys66Gln	NC_000001.10:g.201335973T>G	L. P.	1	1		53	Damaging	Probably damaging	Disease causing	22
TNNT2	NP_001001430.1:p.Phe70Leu	NC_000001.10:g.201334794A>G	L.P.	1	1		22	Tolerated	Probably damaging	Disease causing	19
TNNT2	NP_001001430.1:p.Leu74Phe	NC_000001.10:g.201334780C>A	L.P.	1	1		22	Damaging	Probably damaging	Disease causing	92
TNNT2	NP_001001430.1:p.Ile79Asn	NC_000001.10:g.201334766A>T	P.	7	18	rs121964855	194	Damaging	Probably damaging	Disease causing	65, 66, 67, 68
TNNT2	NP_001001430.1:p.Ile79Thr	NC_000001.10:g.201334766A>G	L.P.	1	1	rs121964855	89	Damaging	Probably damaging	Disease causing	69
TNNT2	NP_001001430.1:p.Pro80Ser	NC_000001.10:g.201334764G>A	L. P.	1	2	rs397516451	74	Damaging	Probably damaging	Disease causing	53
TNNT2	NP_001001430.1:p.Gly82Arg	NC_000001.10:g.201334758C>T	L.P.	2	4	rs727504255	125	Damaging	Probably damaging	Disease causing	70
TNNT2	NP_001001430.1:p.Glu83Lys	NC_000001.10:g.201334755C>T	L.P.	2	4	rs727504244	56	Damaging	Probably damaging	Disease causing	66
TNNT2	NP_001001430.1:p.Glu83Asp	NC_000001.10:g.201334753C>G	L.P.	2	2	rs727503514	45	Tolerated	Benign	Disease causing	44, 71
TNNT2	NP_001001430.1:p.Arg84Thr	NC_000001.10:g.201334751C>G	L.P.	1	1	rs397516452	71	Damaging	Probably damaging	Disease causing	108
TNNT2	NP_001001430.1:p.Arg84Ser	NC_000001.10:g.201334750T>A	L.P.	1	1	rs397516453	110	Damaging	Probably damaging	Disease causing	107
TNNT2	NP_001001430.1:p.Val85Met	NC_000001.10:g.201334749C>T	L.P.	1	2		21	Damaging	Probably damaging	Disease causing	72
TNNT2	NP_001001430.1:p.Val85Leu	NC_000001.10:g.201334749C>G	L.P.	2	2		32	Damaging	Benign	Disease causing	73
TNNT2	NP_001001430.1:p.Asp86Ala	NC_000001.10:g.201334745T>G	L.P.	3	3	rs397516455	126	Damaging	Probably damaging	Disease causing	20
TNNT2	NP_001001430.1:p.Phe87Leu	NC_000001.10:g.201334743A>G	P.	1	11		22	Tolerated	Probably damaging	Disease causing	74
TNNT2	NP_001001430.1:p.Ile90Met	NC_000001.10:g.201334430G>C	P.	2	15		10	Damaging	Probably damaging	Disease causing	75
TNNT2	NP_001001430.1:p.Arg92Trp	NC_000001.10:g.201334426G>A	P.	41	84	rs397516456	101	Damaging	Probably damaging	Disease causing	20, 26, 53, 66, 69, 73, 76, 77, 78, 79, 80, 81, 82

	PROTEIN LEVEL	CHROMOSOMIC LEVEL	PAT.	Index (families)	Affected	RS	G.D.	SIFT	Polyphen-2	Mutation Taster	References
TNNT2	NP_001001430.1:p.Arg92Gln	NC_000001.10:g.201334425C>T	P.	23	64	rs121964856	43	Tolerated	Probably damaging	Disease causing	65, 66, 67, 76, 78, 83, 84, 85, 86
TNNT2	NP_001001430.1:p.Arg92Leu	NC_000001.10:g.201334425C>A	P.	4	8	rs121964856	102	Damaging	Probably damaging	Disease causing	19, 66
TNNT2	NP_001001430.1:p.Arg94Cys	NC_000001.10:g.201334420G>A	P.	4	4	rs727503513	180	Damaging	Probably damaging	Disease causing	53, 73
TNNT2	NP_001001430.1:p.Arg94His	NC_000001.10:g.201334419C>T	L.P.	5	5	rs397516457	29	Damaging	Probably damaging	Disease causing	13, 72
TNNT2	NP_001001430.1:p.Arg94Leu	NC_000001.10:g.201334419C>A	P.	5	7	rs397516457	102	Damaging	Probably damaging	Disease causing	26, 56, 66, 87
TNNT2	NP_001001430.1:p.Glu96Lys	NC_000001.10:g.201334414C>T	L.P.	1	4		56	Damaging	Probably damaging	Disease causing	88
TNNT2	NP_001001430.1:p.Lys97Asn	NC_000001.10:g.201334409C>A	L.P.	2	3	rs397516459	94	Damaging	Probably damaging	Disease causing	89
TNNT2	NP_001001430.1:p.Ala104Val	NC_000001.10:g.201334389G>A	L.P.	3	6	rs727504245	64	Tolerated	Possibly damaging	Polymorphism	63, 66
TNNT2	NP_001001430.1:p.Phe110Ile	NC_000001.10:g.201334372A>T	P.	16	31	rs121964858	21	Damaging	Probably damaging	Disease causing	26, 53, 65, 69, 73, 76, 90
TNNT2	NP_001001430.1:p.Phe110Leu	NC_000001.10:g.201334372A>G	P.	6	8	rs121964858	22	Damaging	Probably damaging	Disease causing	76, 84
TNNT2	NP_001001430.1:p.Phe110Val	NC_000001.10:g.201334372A>C	L.P.	2	7	rs121964858	50	Damaging	Probably damaging	Disease causing	19, 91
TNNT2	NP_001001430.1:p.Lys124Asn	NC_000001.10:g.201334328T>A	L.P.	1	1		94	Damaging	Probably damaging	Disease causing	92
TNNT2	NP_001001430.1:p.Arg126Trp	NC_000001.10:g.201334324T>A	L.P.	1	1	rs786204405	101	Damaging	Probably damaging	Disease causing	16
TNNT2	NP_001001430.1:p.Glu128Lys	NC_000001.10:g.201333503C>T	L.P.	5	5	rs730881100	56	Damaging	Probably damaging	Disease causing	1, 41
TNNT2	NP_001001430.1:p.Arg130Cys	NC_000001.10:g.201333497G>A	P.	11	16	rs397516463	180	Damaging	Probably damaging	Disease causing	26, 69, 76, 84, 92
TNNT2	NP_001001430.1:p.Arg131Trp	NC_000001.10:g.201333494G>A	P.	5	6	rs74315380	101	Damaging	Probably damaging	Disease causing	29, 44, 93, 94
TNNT2	NP_001001430.1:p.Arg134Gly	NC_000001.10:g.201333485G>C	P.	3	11	rs45525839	125	Damaging	Probably damaging	Disease causing	5, 44, 94, 95
TNNT2	NP_001001430.1:p.Arg139His	NC_000001.10:g.201333469C>T	L.P.	1	1	rs397516466	29	Damaging	Probably damaging	Disease causing	94
TNNT2	NP_001001430.1:p.Arg141Trp	NC_000001.10:g.201333464G>A	P.	11	30	rs74315379	101	Damaging	Probably damaging	Disease causing	5, 14, 44, 94, 96
TNNT2	NP_001001430.1:p.Arg144Trp	NC_000001.10:g.201333455G>A	L.P.	1	6	rs483352832	101	Damaging	Probably damaging	Disease causing	97
TNNT2	NP_001001430.1:p.Arg148Trp	NC_000001.10:g.201333443G>A	L. P.	1	1	rs730881123	101	Damaging	Probably damaging	Disease causing	118
TNNT2	NP_001001430.1:p.Arg151Cys	NC_000001.10:g.201333434G>A	L.P.	1	1	rs45608937	180	Damaging	Probably damaging	Disease causing	5, 94, 95
TNNT2	NP_001001430.1:p.Ala157Ser	NC_000001.10:g.201332525C>A	L.P.	2	2		99	Tolerated	Possibly damaging	Disease causing	12, 13
TNNT2	NP_001001430.1:p.Arg159Gln	NC_000001.10:g.201332518C>T	L.P.	2	2	rs45501500	43	Tolerated	Probably damaging	Disease causing	5, 94, 95, 98
TNNT2	NP_001001430.1:p.Glu163Lys	NC_000001.10:g.201332507C>T	L.P.	5	8		56	Tolerated	Possibly damaging	Disease causing	25, 53, 65, 66
TNNT2	NP_001001430.1:p.Ala172Ser	NC_000001.10:g.201332480C>A	L.P.	2	8	rs730881097	99	Tolerated	Probably damaging	Disease causing	81, 99
TNNT2	NP_001001430.1:p.Arg173Trp	NC_000001.10:g.201332477G>A	P.	4	25	rs727503512	101	Damaging	Probably damaging	Disease causing	13, 100
TNNT2	NP_001001430.1:p.Arg173Gln	NC_000001.10:g.201332476C>T	P.	3	9	rs397516471	43	Damaging	Probably damaging	Disease causing	44., 101
TNNT2	NP_001001430.1:p.Ser179Phe	NC_000001.10:g.201332458G>A	L.P.	2	6	rs727504246	155	Damaging	Probably damaging		102

	PROTEIN LEVEL	CHROMOSOMIC LEVEL	PAT.	Index (families)	Affected	RS	G.D.	SIFT	Polyphen-2	Mutation Taster	References
TNNT2	NP_001001430.1:p.Gly186Val	NC_000001.10:g.201332437C>A	L.P.	2	2		109	Damaging	Probably damaging	Disease causing	103
TNNT2	NP_001001430.1:p.Arg205Trp	NC_000001.10:g.201331117G>A	L.P.	4	4	rs45586240	101	Damaging	Probably damaging	Disease causing	5, 45, 95
TNNT2	NP_001001430.1:p.Arg205Gln	NC_000001.10:g.201331116C>T	L. P.	1	4	rs121964860	43	Damaging	Probably damaging	Disease causing	119
TNNT2	NP_001001430.1:p.Arg205Leu	NC_000001.10:g.201331116C>A	L.P.	1	3	rs121964860	102	Damaging	Probably damaging	Disease causing	5, 29, 94
TNNT2	NP_001001430.1:p.Lys217Met	NC_000001.10:g.201331080T>A	L. P.	1	1		95	Damaging	Probably damaging	Disease causing	2
TNNT2	NP_001001430.1:p.Lys247Arg	NC_000001.10:g.201330447T>C	L. P.	2	2		26	Tolerated	Probably damaging	Disease causing	83, 111
TNNT2	NP_001001430.1:p.Lys258Ile	NC_000001.10:g.201330414T>A	L. P.	2	2	rs397516482	102	Damaging	Probably damaging	Disease causing	107, 108
TNNT2	NP_001001430.1:p.Asn262Asp	NC_000001.10:g.201328788T>C	L.P.	1	1		23	Damaging	Probably damaging	Disease causing	78
TNNT2	NP_001001430.1:p.Asn262Ser	NC_000001.10:g.201328787T>C	L.P.	4	4	rs397516483	23	Tolerated	Probably damaging	Disease causing	22, 109, 110
TNNT2	NP_001001430.1:p.Asp270Asn	NC_000001.10:g.201328764C>T	L.P.	1	2	rs121964861	23	Damaging	Probably damaging	Disease causing	29, 94
TNNT2	NP_001001430.1:p.Asn271Ile	NC_000001.10:g.201328760T>A	P.	4	6		149	Tolerated	Probably damaging	Disease causing	16, 19
TNNT2	NP_001001430.1:p.Lys273Glu	NC_000001.10:g.201328755T>C	P.	4	12		56	Damaging	Probably damaging	Disease causing	53, 73, 85
TNNT2	NP_001001430.1:p.Arg278Cys	NC_000001.10:g.201328373G>A	P.	49	65	rs121964857	180	Damaging	Probably damaging	Disease causing	12, 13, 20, 38, 42, 65, 66, 76, 83, 84, 86, 104, 105
TNNT2	NP_001001430.1:p.Arg278His	NC_000001.10:g.201328372C>T	L.P.	1	1	rs397516484	29	Tolerated	Probably damaging	Disease causing	66
TNNT2	NP_001001430.1:p.Arg278Pro	NC_000001.10:g.201328372C>G	P.	4	6	rs397516484	103	Tolerated	Probably damaging	Disease causing	20, 41, 104
TNNT2	NP_001001430.1:p.Arg278Leu	NC_000001.10:g.201328372C>A	L.P.	1	1		102	Tolerated	Probably damaging	Disease causing	78
TNNT2	NP_001001430.1:p.Arg286Cys	NC_000001.10:g.201328349G>A	P.	7	9	rs367785431	180	Damaging	Probably damaging	Disease causing	19, 104, 106
TNNT2	NP_001001430.1:p.Arg286His	NC_000001.10:g.201328348C>T	L.P.	10	12	rs141121678	29	Damaging	Probably damaging	Disease causing	20, 30
TNNT2	NP_001001430.1:p.Arg286Pro	NC_000001.10:g.201328348C>G	L.P.	2	2		103	Damaging	Probably damaging	Disease causing	3

PAT: pathogenicity; **LP**: likely pathogenic; **P:** pathogenic; **Affec:** affected carriers; **G.D:** Grahntam's distance (conservation).

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Supplementary Table 3. Structures of thin filament protein components and complexes.

PDB	Description	Protein	Species	Sequence[a]	Human cardiac sequence[a]
1J1E[b]	Troponin (Ca^{2+}-bound)	Cardiac TnC	Human	P63316:1-161	P63316:1-161
		Cardiac TnT	Human	P45379:212-286	P45379:212-286
		Cardiac TnI	Human	P19429:35-162	P19429:35-162
1YTZ[c]	Troponin (Ca^{2+}-bound)	Skeletal TnC	Chicken	P02588:2-163	P63316:2-161
		Skeletal TnT	Chicken	P12620:160-249	P45379:194-285
		Skeletal TnI	Chicken	P68246:4-144	P19429:35-176
1YV0[c]	Troponin (Ca^{2+}-free)	Skeletal TnC	Chicken	P02588:2-163	P63316:2-161
		Skeletal TnT	Chicken	P12620:160-249	P45379:194-285
		Skeletal TnI	Chicken	P68246:4-119	P19429:35-151
2W4U[d]	Troponin, tropomyosin and actin	Skeletal TnC	Chicken	P02588:5-163	P63316:5-161
		Skeletal TnT	Chicken	P12620:160-249	P45379:194-285
		Skeletal TnI	Chicken	P68246:4-144	P19429:35-176
		Tropomyosin	Rabbit	P58772:8-284	P09493:8-284

		Skeletal actin	Rabbit	P68135:3-374	P68032:3-374
2Z5H[e]	Tropomyosin & TnT	Tropomyosin	Rabbit	P58772:254-284	P09493:254-284
		Skeletal TnT	Chicken	P12520:58-112	P45379:100-133
1VDI[f]	TnI (Ca^{2+}-bound)	Skeletal TnI	Chicken	P68246:132-183	P19429:164-210
1VDJ[f]	TnI (Ca^{2+}-free)	Skeletal TnI	Chicken	P68246:132-183	P19429:164-210

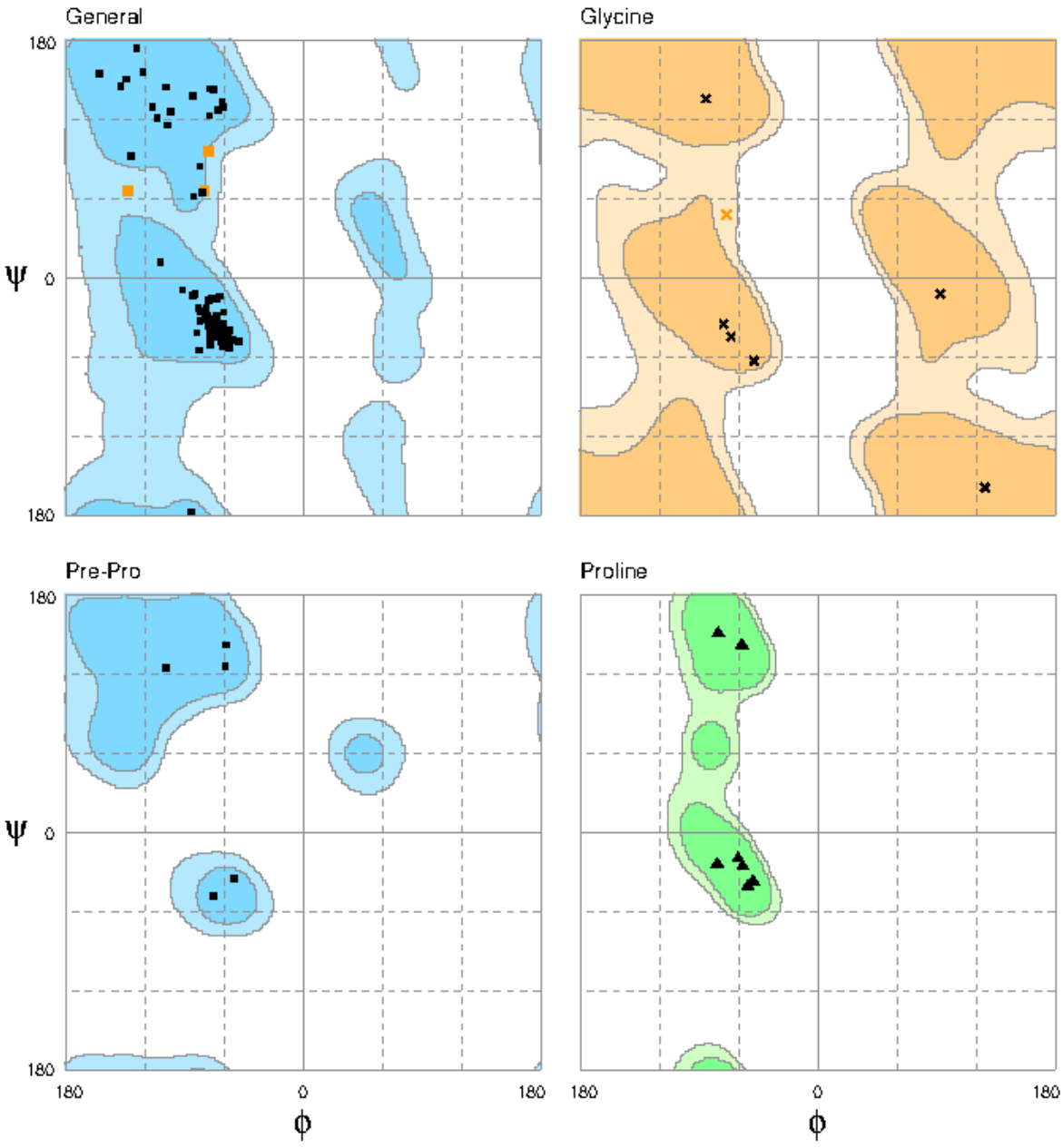
[a] UniProt identifier and sequence range resolved in structure. [b] [PMID:12840750]; [c] [PMID:15784741]; [d] [PMID:22761792]; [e] [PMID:18483193]; [f] [PMID:16061251]

Supplementary Table 4. Estimated penetrance and odds risk calculator in a case-control study of patients harbouring the variants p.Arg278Cys and p.Arg286His in TNNT2.

Variant	HCM Case frequency (variants/total)	GnomAD freq. (variants/total)	Odds ratio	Estimated penetrance	Disease controls freq.	Odds ratio	Estimated penetrance
p.Arg278 Cys	0.71% (62/8,696)	0.071% (98/137,785)	**10.1** (7.33-13.1)	**2.0%** (1.3-3.1)	0.086% (9/10,364)	**4.85** (3.46-6.80)	**1.6%** (0.07-4.0)
p.Arg286 His	0.16% (17/8,696)	0.01% (19/136,988)	**14.4** (7.4-27.2)	**2.8%** (1.1-7)	0.02% (2/10,364)	**10.14** (2.34-43.9)	**2.0%** (0.35-12)

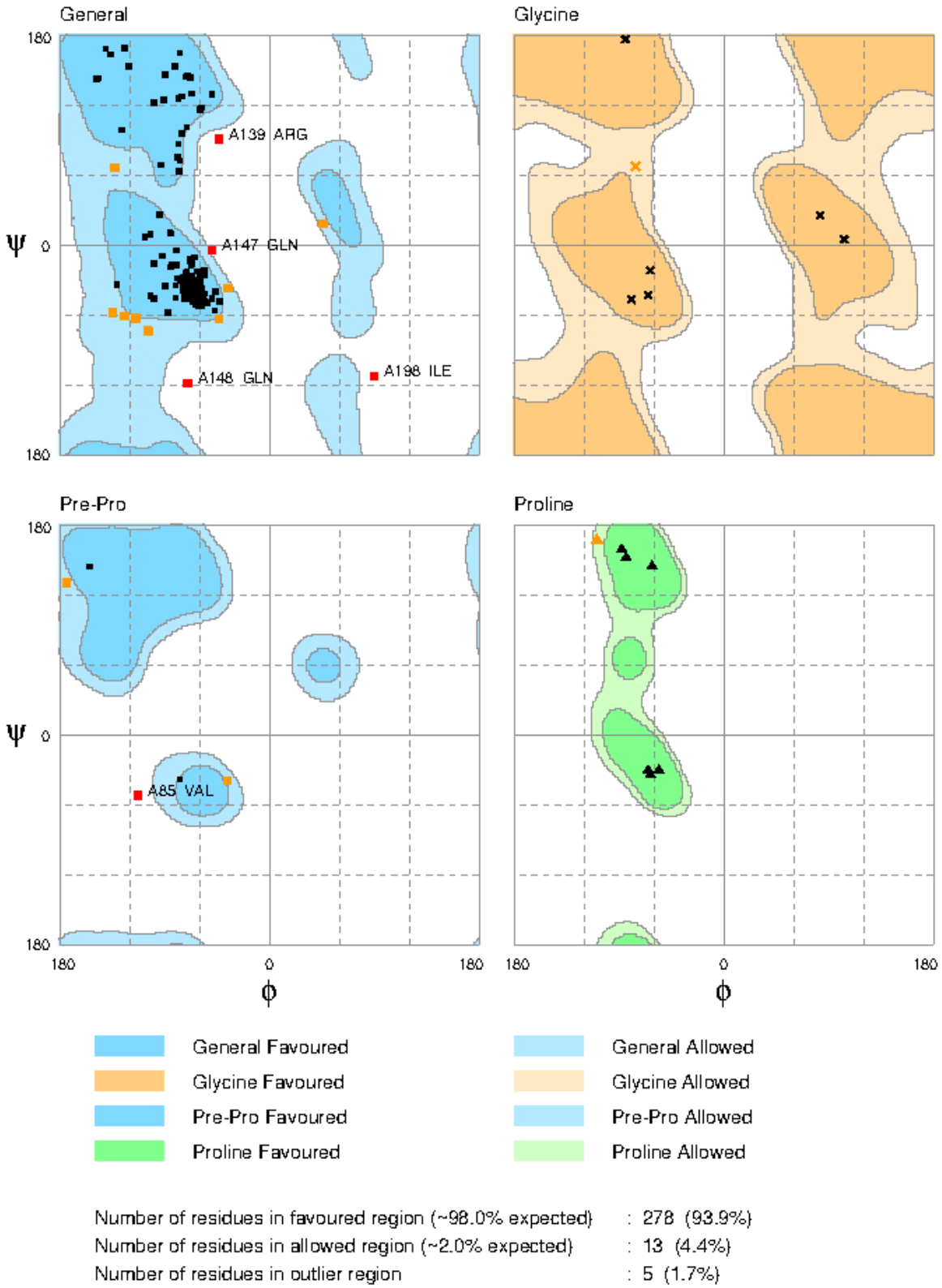
Enrichment of variations p.Arg278Cys and p.Arg286 His in HCM probands compared to controls in the HIC cohort (20,713 probands with different inherited cardiac conditions). Variations are clearly enriched in HCM cohort, with an OR > 5. This adds to these variant the PS4 criteria (strong) that supports the classification of the variations as likely pathogenic.
Penetrance was estimated according the study of Minkel et al. Sci Transl Med. 2016 Jan 20;8(322):322ra9.

Supplementary Figure 4. Ramachandran plot of the cTnT wildtype model 1.



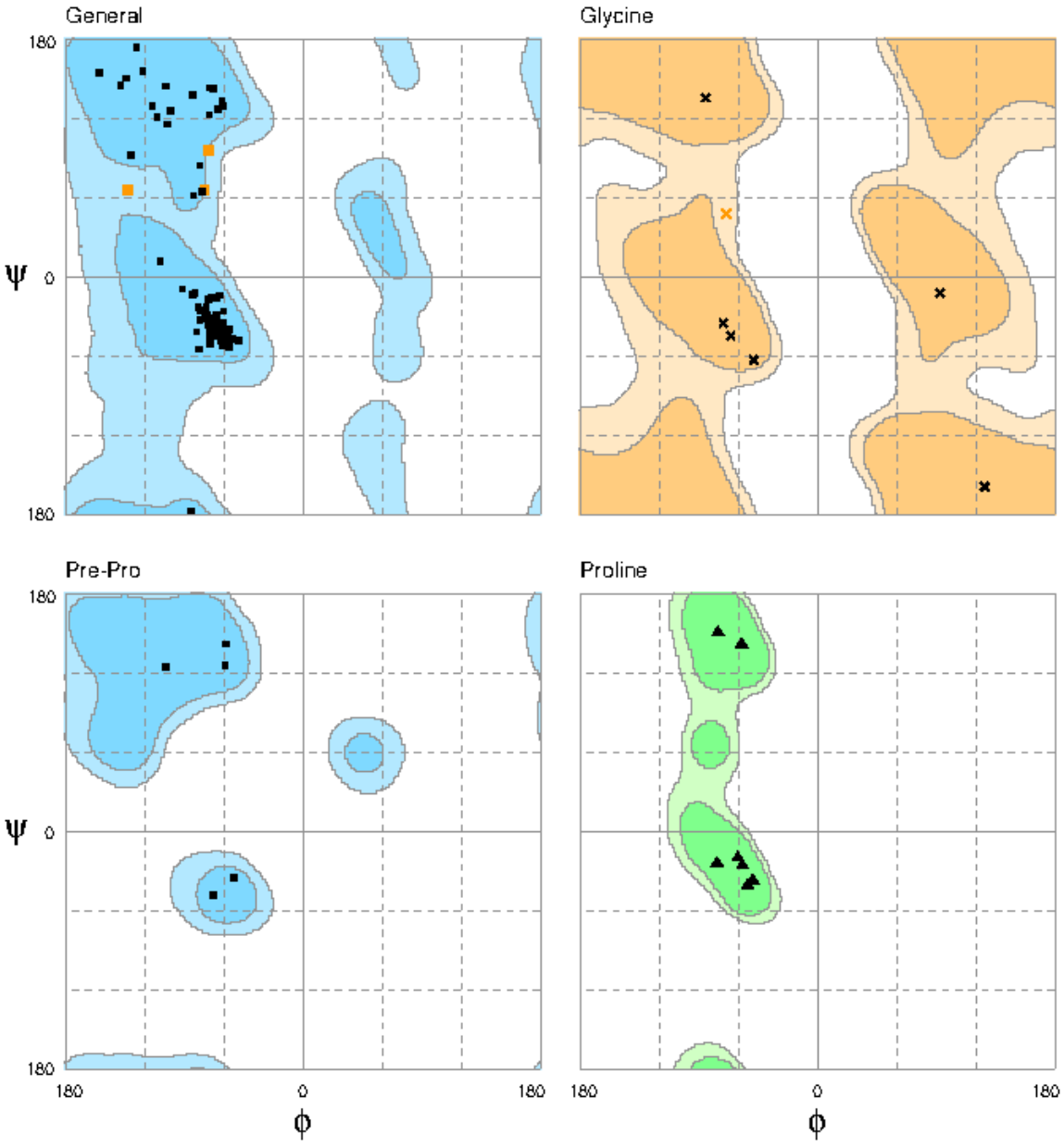
Number of residues in favoured region (~98.0% expected) : 292 (98.6%)
Number of residues in allowed region (~2.0% expected) : 4 (1.4%)
Number of residues in outlier region : 0 (0.0%)

Supplementary Figure 5. Ramachandran plot of the cTnT wildtype model 2.



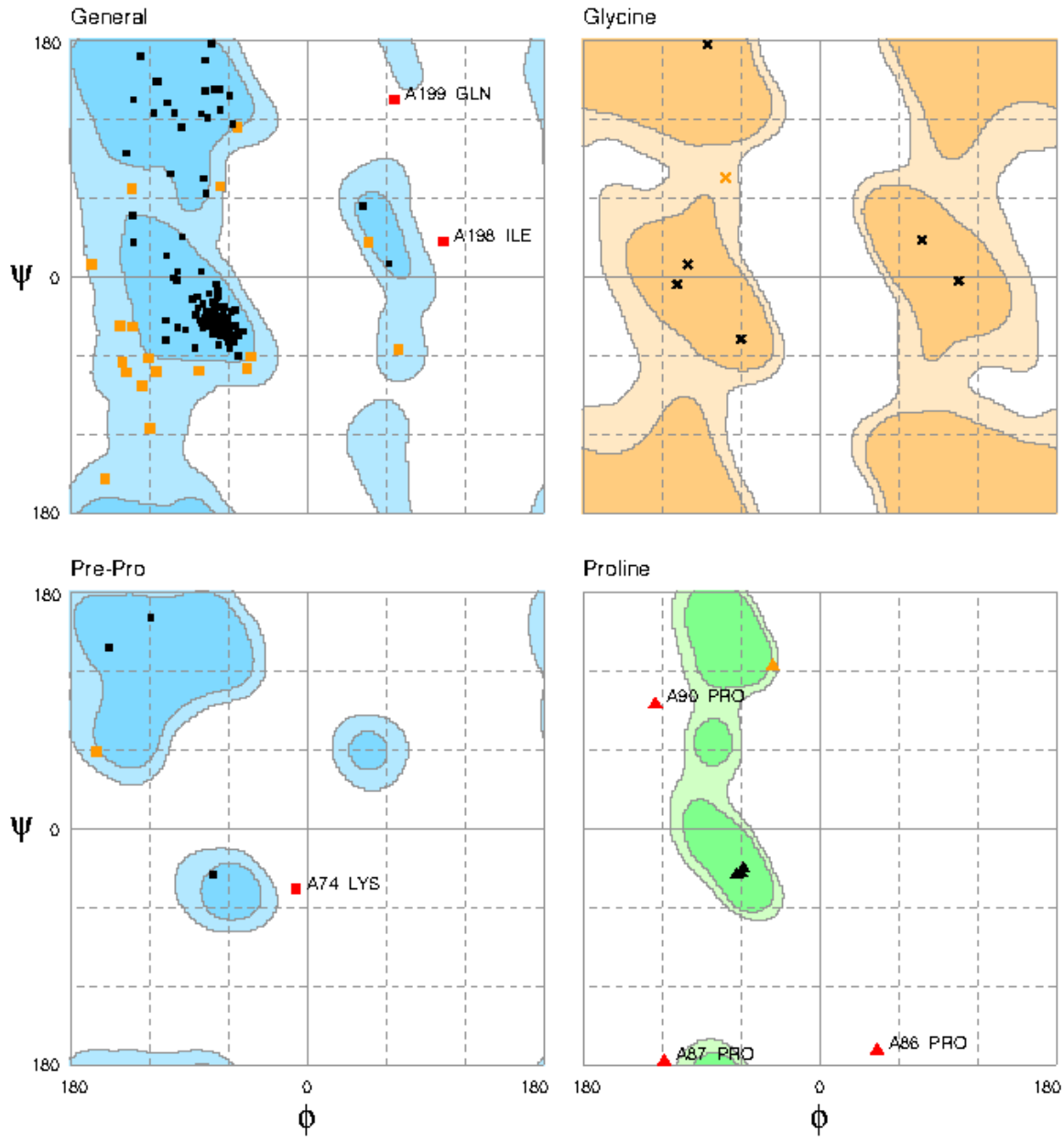
Number of residues in favoured region (~98.0% expected) : 278 (93.9%)
Number of residues in allowed region (~2.0% expected) : 13 (4.4%)
Number of residues in outlier region : 5 (1.7%)

Supplementary Figure 6. Ramachandran plot of the cTnT WT model 3.



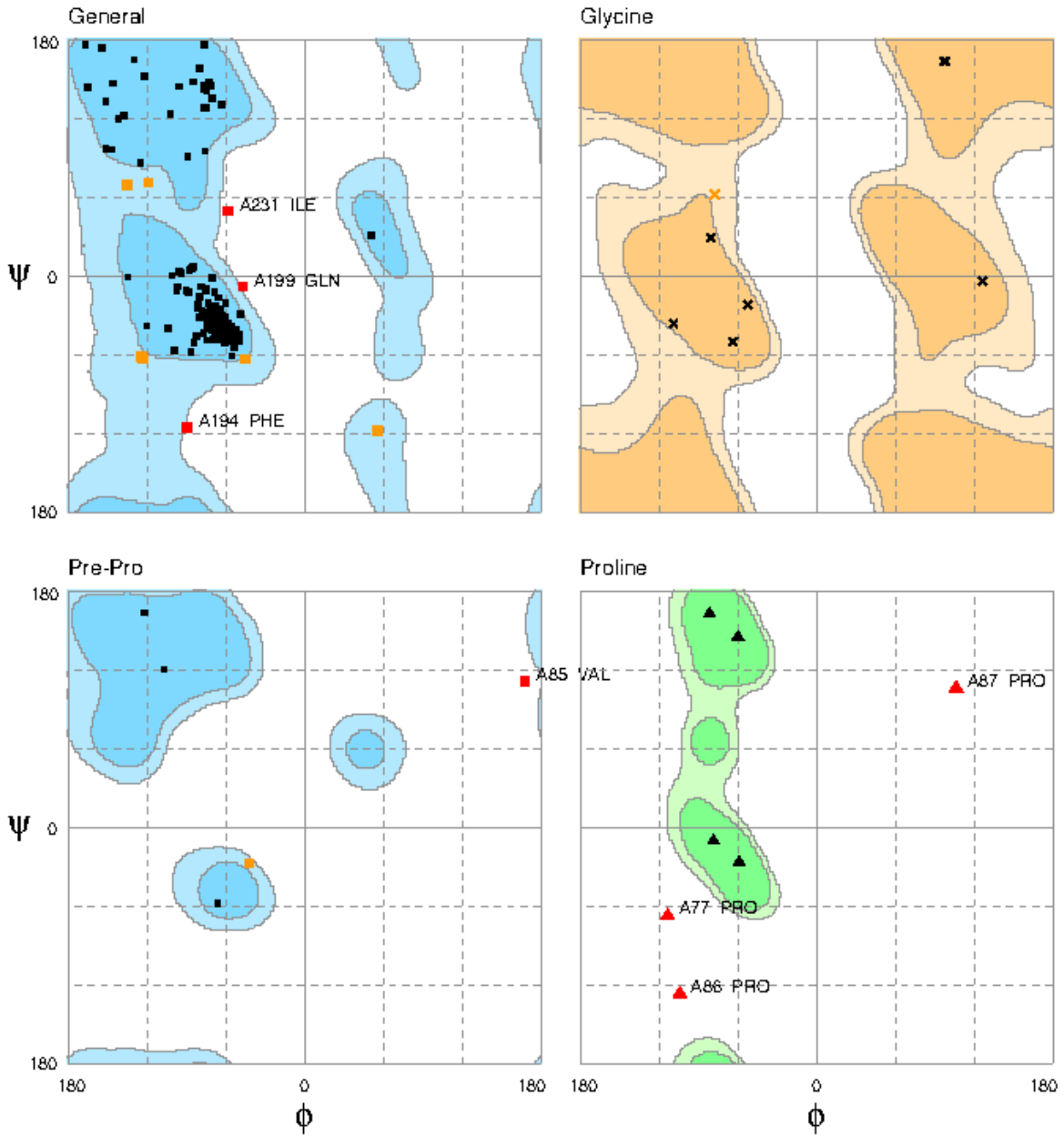
Number of residues in favoured region (~98.0% expected) : 292 (98.6%)
Number of residues in allowed region (~2.0% expected) : 4 (1.4%)
Number of residues in outlier region : 0 (0.0%)

Supplementary Figure 7. Ramachandran plot of the cTnT wildtype model 4.



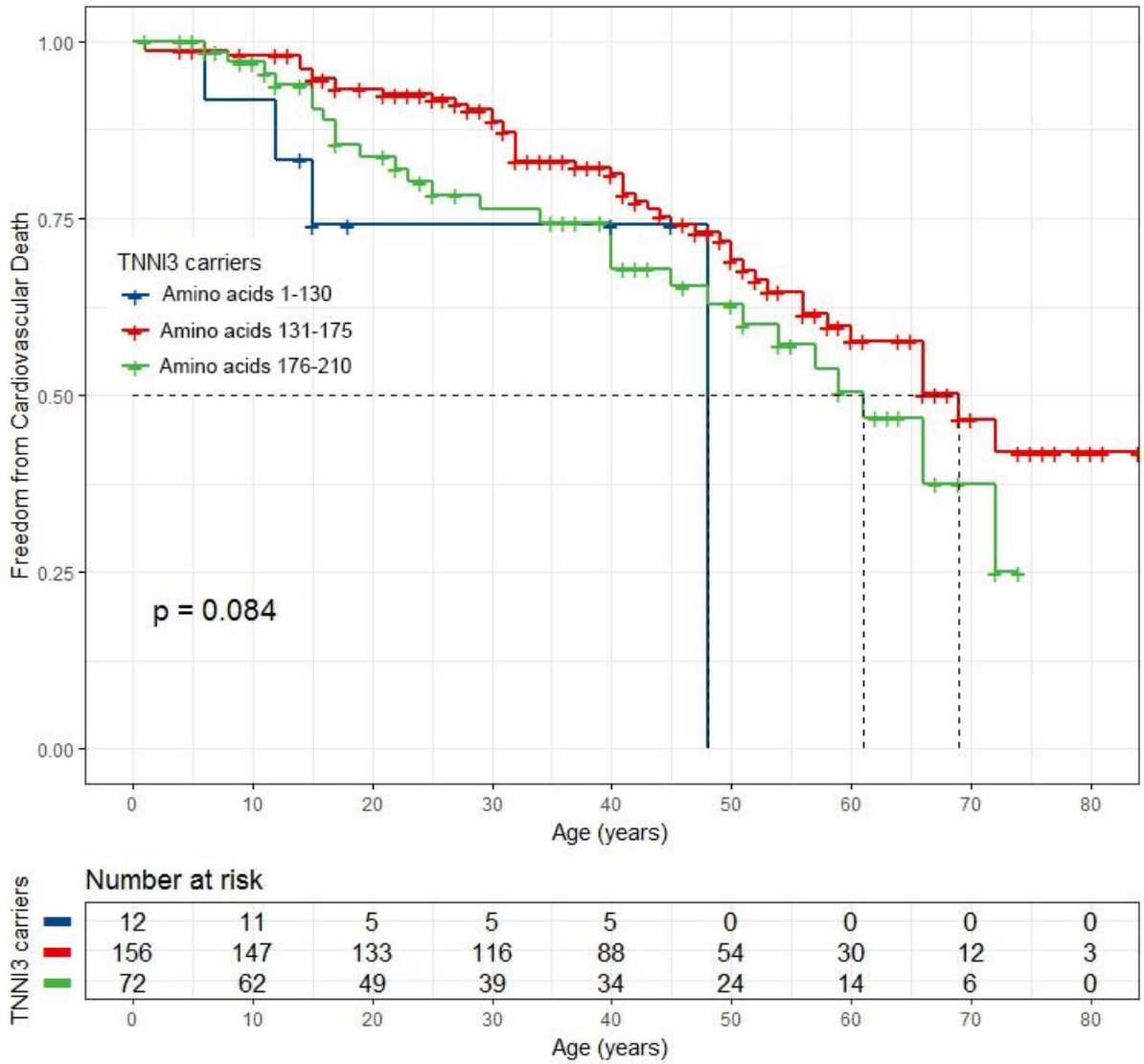
Number of residues in favoured region (~98.0% expected) : 269 (90.9%)
Number of residues in allowed region (~2.0% expected) : 21 (7.1%)
Number of residues in outlier region : 6 (2.0%)

Supplementary Figure 8. Ramachandran plot of the cTnT wildtype model 5.



Number of residues in favoured region (~98.0% expected)	: 281 (94.9%)
Number of residues in allowed region (~2.0% expected)	: 8 (2.7%)
Number of residues in outlier region	: 7 (2.4%)

Supplementary Figure 9. Comparison of the survival from cardiovascular death in carriers of variants in TNNI3 according to regions.



Comparison of the regions involving amino acids 1-130 (blue), 131-175 (red), and 176-210 (green). There were no statistically significant differences between the three regions in terms of survival of cardiovascular death (p=0.084), but data were scarce for patients in region 1-

130.

Pairwise comparison between regions 131-275 and 176-210 showed a worst survival for the later (p=0.008), with medians of survival of 61 and 69 years respectively.

Supplementary Movie 1. Dominant motions in WT cTnT.

https://drive.google.com/file/d/1kIR6M8bZhCe0ClCQeR2X_8Fu6_McD6GM/view

Supplementary Movie 2. Dominant motions in R102Q cTnT.

https://drive.google.com/file/d/1D_quD1E-2kjaU4KYTFU3JOTW4LlT7qWa/view

Supplementary Movie 3. Dominant motions in R102W cTnT.

https://drive.google.com/file/d/1C-g1lPhqJQBZ1Qy5cgrEfYsryWIpUTGp/view

Supplementary Movie 4. Dominant motions in R141W cTnT.

https://drive.google.com/file/d/1HfQbantc04nqAZsItVMP53b9fNLZDjUF/view

Supplementary Movie 5. Dominant motions in R173W cTnT.

https://drive.google.com/file/d/1meA85SIjSxMXwb6pYjiNK5Smez6qHYCb/view