Supplemental Material

Escobar-Lopez et al.

Clinical Risk Score to Predict Pathogenic Genotypes in Patients with Dilated Cardiomyopathy

Online supplementary methods. Variant classification and rules applied for categorization.

Rare genetic variants detected in probands were centrally assessed for pathogenicity and subsequently classified as pathogenic, likely pathogenic, variant of uncertain significance, likely benign or benign by expert assessment using modified criteria of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) guidelines, following the recommendations of the ClinGen Guidelines for Variant Interpretation in Dilated Cardiomyopathy (Morales A. et al. Variant interpretation for dilated cardiomyopathy. Circulation: Genomic and Precision Medicine, 43–51.).

The following ACMG/AMP modified rules were applied:

Population frequency:

PM2: Applied if the filtering allele frequency in the Genomes Aggregation Database (gnomAD) exomes dataset (version 2.1) was below 0.004%, and if the variant was absent from a cohort of disease controls of Spanish origin (Health in Code database).

BS1: Applied if the filtering allele frequency in the gnomAD exomes dataset (version 2.1) was ≥ 0.05%.

BA1: Applied if the filtering allele frequency in the gnomAD exomes dataset (version 2.1) was > 0.1%.

General rules:

PVS1: Truncating variants, i.e., frameshift, nonsense, splice donor and splice acceptor variants, initiation codon, single or multi-exon deletion in the following genes in which LOF is a proven mechanism of disease: *DSP, PKP2, LMNA, MYBPC3, FHL1, DMD*.

PVS1_Strong: Truncating variants, i.e., frameshift, nonsense, splice donor and splice acceptor variants, initiation codon, single or multi-exon deletion in the following genes in which LOF is a proven mechanism of disease: *DSG2, DSC2, FLNC, TNNT2, PLN, TBX20, NKX2-5, PRDM16*. In *TTN*, the rule only applied if the variant affected the A band and/or constitutive exons in the adult cardiac N2B isoform (more than 95% of exon usage -transcript incorporation- in human adult left ventricle).

PM4/BP3: A protein length change because of an in-frame deletion or insertion in a non-repeat region or within a region annotated by repeat masker.

PS1: Same amino acid change as a previously established pathogenic variant (multiple ClinVar submissions with no conflicting evidence).

PM5: Novel missense change at an amino acid residue where a different missense change has previously been established as pathogenic (multiple ClinVar submissions with no conflicting evidence).

PM1: Located in a mutational hot spot and/or critical and well-established functional domain (e.g., active site of an enzyme) without benign variation. This rule applied only for non-truncating rare variants (PM2 rule activated) present in genes that had regions/domains in which all missense variants in these domains identified to date have been shown to be pathogenic and specifically associated with DCM. The rules applied only for RBM20 (amino acid 630-640 and 910-920), and TNNT2 (residues 131-179). We considered that in the remaining genes the information in relation to DCM was insufficient to apply this rule, and that the information based on other phenotypes (i.e., HCM) should not be extrapolated.

Case-control analysis and probands with a consistent phenotype (only one of the following rules can be activated):

PS4: Two scenarios are contemplated:

A. Variants enriched in case cohorts compared with population controls. The DCM cohort used was the Health in Code, A Coruña, Spain, comprising up to 6179 probands (enrichment was defined as a Fisher's exact test $P < 1.79 \times 10^{-6}$, after multiple testing correction). PS4 was also applied for any additional variants enriched in the DCM cohort described in this study (present in ≥ 3 cases and $P < 1.9 \times 10^{-4}$ after Bonferroni multiple testing correction).

B. ≥ 15 probands with a consistent confirmed phenotype (DCM). Applies only for very rare variants (PM2 criteria met).

PS4_Moderate: Variant identified in ≥ 6 probands with consistent confirmed phenotypes (DCM). Only applicable if the variant is absent or rare in large population studies (PM2 criteria met).

PS4_Supporting: Variant identified in ≥ 2 probands with consistent confirmed phenotypes (DCM). Only applicable if the variant is absent or rare in large population studies (PM2 criteria met).

Cosegregation rules (only one of the following rules can be activated):

PP1_Strong: Cosegregation with disease in ≥ 7 segregations in affected family members in a gene definitively known to cause the disease (present in ClinGen curation for DCM). Only applicable if the variant is also absent or rare in large population studies (PM2 criteria met).

PP1_Moderate: Cosegregation with disease in ≥ 5 segregations in affected family members in a gene definitively known to cause the disease (present in ClinGen curation for DCM). Only applicable if the variant is also absent or rare in large population studies (PM2 criteria met).

PP1: Cosegregation with disease in ≥ 3 segregations in affected family members in a gene definitively known to cause the disease (present in ClinGen curation for DCM). Only applicable if the variant is also absent or rare in large population studies (PM2 criteria met).

De novo rules:

PS2: *De novo* (paternity confirmed) in a patient with the disease and no family history (FH) (no suspicion of cardiomyopathy through three generations, and parents have been thoroughly clinically evaluated without evidence suggestive of cardiomyopathy). Only applicable in the ABSENCE of any other possible disease-causing variants.

PM6: Confirmed *de novo*, but without confirmation of paternity or maternity. Both parents must have been tested and shown not to carry the variant, but clinical evaluation of parents is not required.

Functional studies and predictors:

PS3: Well-established *in vitro* or *in vivo* functional studies supportive of a damaging effect on the gene or gene product. Mammalian variant-specific knock-in models or cell model (or other *in vitro* assay) that produces a cellular phenotype that reliably predicts clinical DCM, or causality is demonstrated with appropriate controls (e.g., correction of the variant reverses the phenotype).

PP3/BP4: Multiple lines of computation evidence support or refute a deleterious effect.

For missense variants, CADD, DANN, FATHMM, Polyphen-2, and MutationTaster were used. The rule applied if 4/5 predictors yielded the same result on the impact on the protein.

For intronic variants out of the splicing consensus site (+1, +2, -1, -2) the following predictors were used: SSF, MaxEnt, NNSplice, GeneSplicer and AdaBoost. The rule applied if 4/5 predictors yielded the same result on the impact on splicing.

Online Table 1. Distribution of the disease-causing affected genes in patients with a positive genetic test result in the derivation cohort (*n* = 377)

Affected Gene	Frequency	Percent
TTN	143	37.93
LMNA	33	8.75
DSP	32	8.49
BAG3	24	6.37
RBM20	22	5.84
FLNC	21	5.57
DMD	19	5.04
MYH7	19	5.04
MYBPC3	18	4.77
TNNT2	13	3.45
PKP2	6	1.59
TPM1	5	1.33
TNNI3	4	1.06
DSG2	3	0.80
TBX20	3	0.80
ACTC1	2	0.53
PLN	2	0.53
DSC2	1	0.27
EMD	1	0.27
FKRP	1	0.27
JPH2	1	0.27
PRDM16	1	0.27
SGCD	1	0.27
TMEM43	1	0.27
TNNC1	1	0.27
Total	377	100.00

Online Table 2. Distribution of affected genes in probands with concomitant skeletal myopathy in the derivation cohort (*n* = 36)

Affected gene	Frequency	Percent
BAG3	1	2.8%
DMD	7	19.4%
FKRP	1	2.8%
LMNA	7	19.4%
MYBPC3	3	8.3%
MYH7	2	5.6%
TTN	1	2.8%
PRDM16	1	2.8%
Genotype-negative	13	36.1%
Total	**36**	**100.00%**

Online Table 3. Internal validation: Final model adjusted by bootstrap shrinkage

	Odds Ratio (95% CI)	***P*-value**
FH of DCM	2.18 (1.67-2.84)	<0.001
Skeletal muscle disease	3.17 (1.56-6.46)	0.001
LBBB (absence of)	3.31 (2.42-4.53)	<0.001
Low QRS voltage limb leads	3.34 (2.25-4.94)	<0.001
Hypertension (absence of)	2.17 (1.62-2.91)	<0.001
_cons (baseline odds)	0.08 (0.07-0.09)	<0.001

Online Table 4. Distribution of the disease-causing affected genes in patients with a positive genetic test result in the validation cohort (*n* = 289)

Affected Gene	Frequency	Percent
TTN	143	49.00
FLNC	26	8.90
LMNA	25	8.56
TNNT2	24	8.22
MYH7	14	4.79
DSP	11	3.77
RBM20	7	2.40
DMD	5	1.71
SCN5A	5	1.71
BAG3	4	1.37
DSC2	4	1.37
TPM1	4	1.37
DSG2	3	1.03
MYBPC3	3	1.03
ACTC1	2	0.68
DES	2	0.68
PKP2	2	0.68
PLN	2	0.68
EMD	1	0.34
PRDM16	1	0.34
TNNC1	1	0.34
Total	289	100.00

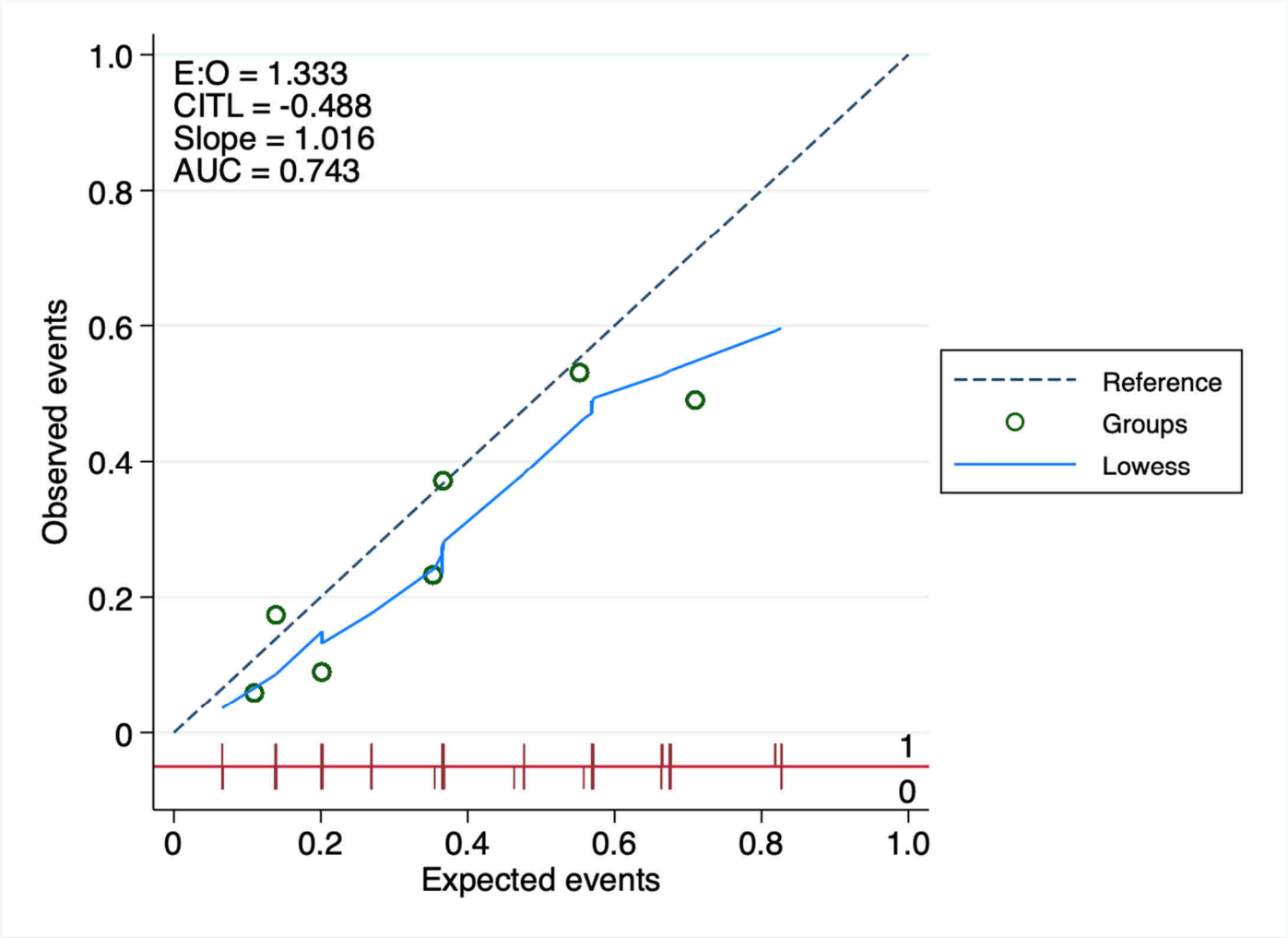
Online Table 5. Distribution of affected genes in probands with concomitant skeletal myopathy in the validation cohort (*n* = 15)

Affected gene	Frequency	Percent
DMD	3	20.0%
EMD	1	6.7%
FLNC	1	6.7%
LMNA	2	13.3%
MYH7	1	6.7%
TTN	2	13.3%
Genotype-negative	5	33.3%
Total	**15**	**100.00%**

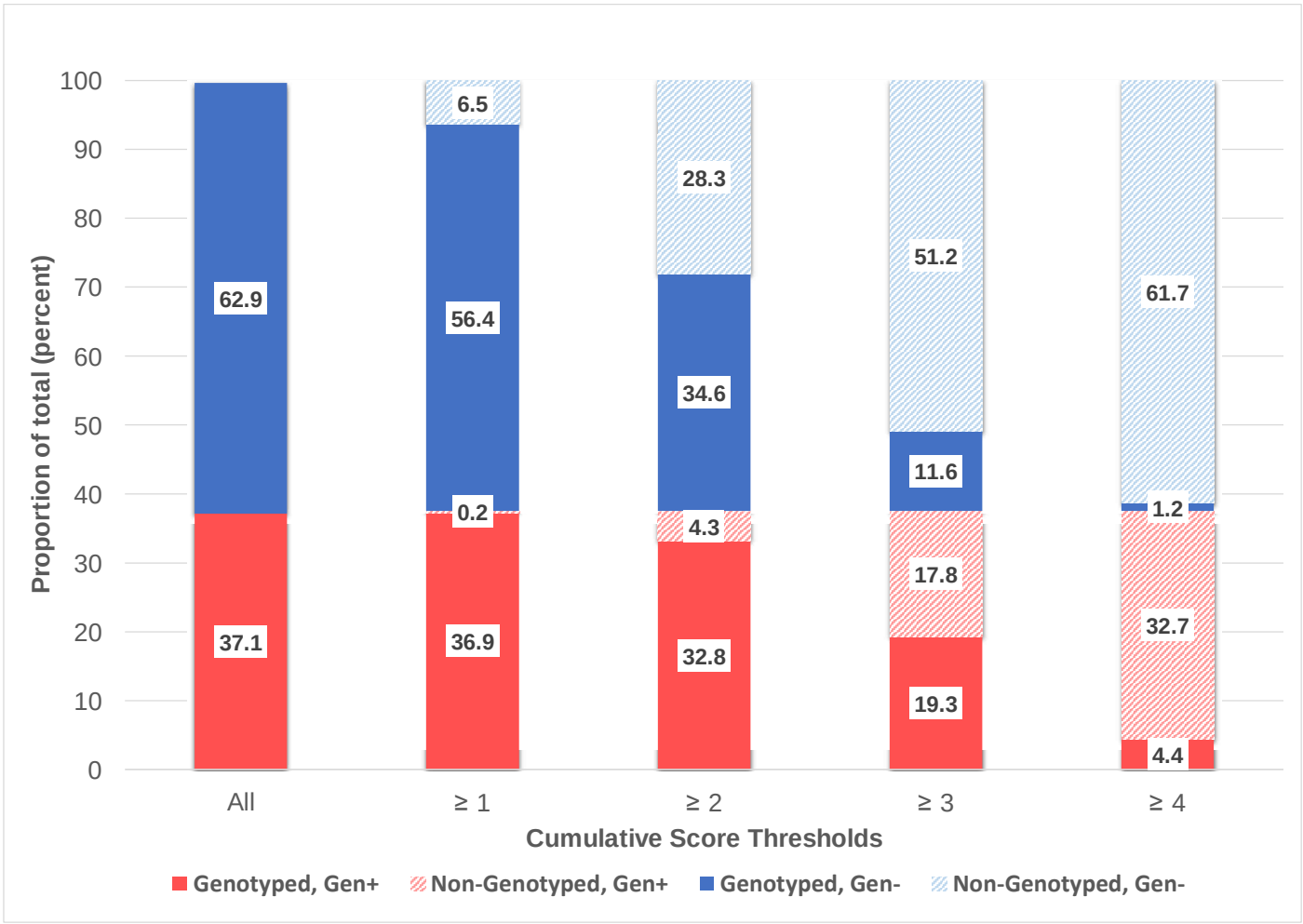
Online Table 6. Predicted probability for all-sets

Family history of DCM	Skeletal myopathy	Absence of LBBB	Low QRS voltage on limb leads	Absence of hypertension	Predicted probability
No	No	No	No	No	0.0657
No	No	No	No	Yes	0.1385
Yes	No	No	No	No	0.1389
No	No	Yes	No	No	0.2013
No	No	No	Yes	No	0.2027
Yes	No	No	No	Yes	0.2693
No	Yes	No	No	Yes	0.3550
Yes	Yes	No	No	No	0.3559
No	No	Yes	No	Yes	0.3655
Yes	No	Yes	No	No	0.3664
No	No	No	Yes	Yes	0.3674
Yes	No	No	Yes	No	0.3683
No	Yes	Yes	No	No	0.4633
No	No	Yes	Yes	No	0.4767
Yes	Yes	No	No	Yes	0.5580
Yes	No	Yes	No	Yes	0.5692
Yes	No	No	Yes	Yes	0.5712
No	Yes	Yes	No	Yes	0.6636
Yes	Yes	Yes	No	No	0.6644
No	No	Yes	Yes	Yes	0.6755
Yes	No	Yes	Yes	No	0.6763
Yes	Yes	Yes	No	Yes	0.8190
Yes	No	Yes	Yes	Yes	0.8268
No	Yes	Yes	Yes	Yes	0.8770
Yes	Yes	Yes	Yes	Yes	0.9424

Online Figure 1. External validation. C-Statistic = 0.743, 95%CI 0.711-0.775



Online Figure 2. Results of genetic testing in the derivation cohort according to the Madrid DCM genotype score thresholds



The bars show the impact of using different score thresholds to select patients for genotyping. Each bar represents the complete derivation cohort (n = 1015) and color-coding represents the proportion of patients classified as genotype-positive (red) and genotype-negative (blue) as well as individuals who would have been genotyped (solid color) or not genotyped (striped color) according to each threshold.

Candidate variables and definitions:

1. Sex.
2. Age at diagnosis.
3. Hypertension: Hypertension preceding DCM diagnosis or diagnosed at the first evaluation. In accordance with most major guidelines, hypertension is diagnosed when a person's systolic blood pressure in the office or clinic is ≥ 140 mm Hg and/or their diastolic blood pressure is ≥ 90 mm Hg following repeated examination. (Reference: European Heart Journal: doi/10.1093/eurheartj/ehy339, Hypertension: doi.org/10.1161/HYPERTENSIONAHA.120.15026).
4. Diabetes: Diabetes preceding DCM diagnosis or diagnosed at the first evaluation according to the diagnosis criteria of the guidelines of the American Diabetes Association: doi.org/10.2337/dc19-S002, Diabetes Care 2019 Jan; 42(Supplement 1): S13-S28.
5. Smoking history: Current or former smoker according to World Health Organization (WHO) definition.
6. Hypercholesterolemia: According to WHO definition.
7. Skeletal muscle disease: Clinically diagnosed myopathy by a neurologist based on physical examination findings, electromyography, or histopathological alterations at initial cardiac evaluation.
8. FH of DCM: family history of non-ischemic DCM (excluding severe valvular heart disease) in any first-, second-, or third-degree relative.
9. FH of sudden cardiac death (SCD) in a first-degree relative: History of SCD in a first-degree relative <50 years of age with SCD deemed definitely or likely due to DCM.
10. FH of SCD in a non-first-degree relative: History of SCD in a non-first-degree relative <50 years of age with SCD deemed definitely or likely due to DCM.
11. FH of skeletal myopathy: History of clinically diagnosed skeletal myopathy in a first-degree or close relative <50 years of age.
12. LBBB: QRS duration > 0.12 sec with a LBBB pattern on the baseline ECG.
13. AV block (any degree) at baseline: Observed on the baseline ECG.
14. Atrial fibrillation: History of atrial fibrillation at initial evaluation.
15. Abnormal T-wave inversion: Negative T-wave of ≥ 1 mm in depth in two or more contiguous leads with exclusion of leads aVR, III and V1 on the baseline ECG.
16. Low QRS voltage limb leads: QRS amplitude ≤ 5 mm (0.5 mV) in all limbs leads on the baseline ECG.
17. Low QRS voltage precordial leads: QRS amplitude ≤ 10 mm (10 mV) in all precordial leads on the baseline ECG.
18. Baseline LVEF: Left ventricular ejection fraction measured by 2-dimensional echocardiography at the baseline assessment.

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List of pathogenic and likely pathogenic variables identified in the derivation cohort

Gene	Transcript	Protein change	Variant type	Number of probands (this cohort)	HIC controls (FAF) n alelles = 10,508	gnomAD FAF popmax	ACMG rules	ACMG clasification
ACTC1	NM_005159.4	p.Asp4His	Missense	1	0	0	PM2,PP2,PP3,PP4,PS4_Supporting,	LP
ACTC1	NM_005159.4	p.Met271Val	Missense	1	0	0	PM2,PP2,PP3,PP4,PS4_Supporting,	LP
BAG3	NM_004281.3	p.Ala128Glufs*84	Frame-shift	1	0	0	PVS1,PM2,PS4_Moderate,PP1,	P
BAG3	NM_004281.3	p.Ala176Hisfs*31	Frame-shift	1	0	0	PVS1,PM2,	LP
BAG3	NM_004281.3	p.Arg121*	Nonsense	1	0	0	PVS1,PM2,PS4_Moderate,	P
BAG3	NM_004281.3	p.Arg301Serfs*6	Frame-shift	2	0	0	PVS1,PM2,PP1,PP5,	P
BAG3	NM_004281.3	p.Arg309*	Nonsense	3	0	0	PVS1,PM2,PS4_Moderate,PP1,PP5,	P
BAG3	NM_004281.3	p.Gln116*	Nonsense	1	0	0	PVS1,PM2,	LP
BAG3	NM_004281.3	p.Gln132*	Nonsense	1	0	0	PVS1,PM2,	LP
BAG3	NM_004281.3	p.Gln153*	Nonsense	1[#]	0	0	PVS1,PM2,PP1,	P
BAG3	NM_004281.3	p.Gln88*	Nonsense	1	0	0	PVS1,PM2,PP5,	P
BAG3	NM_004281.3	p.Glu471Lys	Missense	2	0	0,000016	PM1,PM2,PP3,PP5,	LP
BAG3	NM_004281.3	p.Glu543Lysfs*23	Frame-shift	2	0	0	PVS1,PM2,	LP
BAG3	NM_004281.3	p.His232Thrfs*75	Frame-shift	1	0	0	PVS1,PM2,	LP
BAG3	NM_004281.3	p.His243Thrfs*64	Frame-shift	3	0	0	PVS1,PP1_Strong,PM2,PS4_Supporting,	P
BAG3	NM_004281.3	p.Pro137Glyfs*72	Frame-shift	3	0	0	PVS1,PM2,PS4_Supporting,	P
BAG3	NM_004281.3	p.Pro402Leufs*22	Frame-shift	1	0	0	PVS1,PM2,	LP
BAG3	NM_004281.3	p.Trp36*	Nonsense	1	0	0	PVS1,PM2,PP5,PS4_Supporting,	P
DMD	NM_004006.2	c.264+2_264+3insT	Splicing	1	0	0	PVS1,PM2,PP4,	P
DMD	NM_004006.2	c.4072-1G>A	Splicing	1	0	0	PVS1,PM2,PS4_Supporting,	P
DMD	NM_004006.2	Del exon 10 to 12	Deletion	1	0	0	PVS1,PM2,PS4_Supporting,	P
DMD	NM_004006.2	Del exon 25 to 30	Deletion	1	0	0	PVS1,PM2,PP4,	P
DMD	NM_004006.2	Del exon 3 to 9	Deletion	1	0	0	PVS1,PM2,PS4_Supporting,	P
DMD	NM_004006.2	Del exon 44 to 53	Deletion	1	0	0	PVS1,PM2,PS4_Supporting,	P
DMD	NM_004006.2	Del exon 45	Deletion	1	0	0	PVS1,PM2,PS4_Supporting,	P
DMD	NM_004006.2	Del exon 45 to 47	Deletion	2	0	0	PVS1,PM2,PP4,	P
DMD	NM_004006.2	Del exon 46 to 47	Deletion	2	0	0	PVS1,PM2,PP4,	P
DMD	NM_004006.2	Del exon 46 to 50	Deletion	1	0	0	PVS1,PM2,PS4_Supporting,	P
DMD	NM_004006.2	Del exon 48 to 50	Deletion	1	0	0	PVS1,PM2,PS4_Supporting,	P
DMD	NM_004006.2	Del exon 48 to 51	Deletion	3	0	0	PVS1,PM2,PS4_Supporting,	P
DMD	NM_004006.2	Del exon 8 to 30	Deletion	1	0	0	PVS1,PM2,PP4,	P
DMD	NM_004006.2	Dup exon 56 to 59	Deletion	1	0	0	PVS1,PM2,PS4_Supporting,	P
DMD	NM_004006.2	p.Lys19Argfs*18	Frame-shift	1	0	0	PVS1,PM2,PP4,	P

Gene	Transcript	Protein change	Variant type	Number of probands (this cohort)	HIC controls (FAF) n alelles = 10,508	gnomAD FAF popmax	ACMG rules	ACMG clasification
DSC2	NM_024422.4	p.Arg375*	Nonsense	1	0	0,00003	PVS1_Strong,PM2,PP5,PS4_Supporting,	P
DSG2	NM_001943.5	p.Gln1114*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
DSG2	NM_001943.4	p.Glu156Argfs*14	Frame-shift	1[#]	0	0,00003	PVS1_Strong,PM2,PP5,	P
DSG2	NM_001943.5	p.Lys141Asnfs*3	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
DSG2	NM_001943.5	p.Pro142Thr	Missense	1	0	0,00003	PM2,PP1,PP3,PS4_Supporting,	LP
DSP	NM_004415.3	c.1045-1G>A	Splicing	1	0	0	PVS1,PM2,	LP
DSP	NM_004415.3	c.1267-2A>G	Splicing	1	0	0	PVS1,PM2,PS4_Supporting,	P
DSP	NM_004415.3	c.2130+1G>A	Splicing	1	0	0	PVS1,PM2,	LP
DSP	NM_004415.3	c.2131-1G>T	Splicing	1	0	0	PVS1,PM2,	LP
DSP	NM_004415.3	c.939+1G>A	Splicing	1	0	0	PVS1,PM2,PP1_Moderate,PP5,PS4_Supporting,	P
DSP	NM_004415.3	Del exon 21 a 23	Deletion	2	0	0	PVS1,PM2,PS4_Supporting,	P
DSP	NM_004415.3	Del exon 9 a 24	Deletion	1	0	0	PVS1,PM2,	LP
DSP	NM_004415.3	p.Arg1045*	Nonsense	1	0	0	PVS1,PM2,PP5,	P
DSP	NM_004415.3	p.Arg1236Thrfs*13	Missense	1	0	0	PVS1,PM2,	LP
DSP	NM_004415.3	p.Arg1951*	Nonsense	1	0	0	PVS1,PM2,PP5,	P
DSP	NM_004415.3	p.Arg451His	Missense	4	0	0	PM2,PM5,PP3,PS4_Supporting,	LP
DSP	NM_004415.3	p.Asp1587Thrfs*15	Frame-shift	1	0	0	PVS1,PM2,	LP
DSP	NM_004415.3	p.Asp2146Metfs*8	Frame-shift	1	0	0	PVS1,PM2,	LP
DSP	NM_004415.3	p.Asp2521Glufs*39	Frame-shift	1	0	0,00002	PVS1,PM2,	LP
DSP	NM_004415.3	p.Gln1567*	Nonsense	1	0	0	PVS1,PM2,	LP
DSP	NM_004415.3	p.Gln1667Hisfs*14	Frame-shift	2	0	0	PVS1,PM2,PP1_Moderate,PS4_Supporting,	P
DSP	NM_004415.3	p.Gln447*	Nonsense	3	0	0	PVS1,PM2,PS4_Supporting,	P
DSP	NM_004415.3	p.Gly36Alafs*12	Frame-shift	1	0	0	PVS1,PM2,	LP
DSP	NM_004415.3	p.Ile1483Asnfs*14	Frame-shift	1	0	0	PVS1,PM2,	LP
DSP	NM_004415.3	p.Leu1773Tyrfs*8	Frame-shift	2	0	0	PVS1,PM2,PS4_Moderate,	P
DSP	NM_004415.3	p.Leu547Trpfs*8	Frame-shift	1	0	0	PVS1,PM2,	LP
DSP	NM_004415.3	p.Leu784*	Nonsense	1	0	0	PVS1,PM2,	LP
DSP	NM_004415.3	p.Lys1564Asnfs*13	Frame-shift	1	0	0	PVS1,PM2,	P
DSP	NM_004415.3	p.Tyr739Valfs*7	Frame-shift	1	0	0	PVS1,PM2,	P
EMD	NM_000117.2	p.Val26Ala	Missense	1	0	0	PS4,PP1_Strong,PM2,PP3,	P
FKRP	NM_024301.4	p.Pro89Ser	Missense	1[#]	0	0,00003	PM3, PM2, PP3, PP4	LP
FKRP	NM_024301.4	p.Val300Ala	Missense	1[#]	0	0,00037	PM2,PM3,PP3,PP4,	LP
FLNC	NM_001458.4	c.2929+5G>A	Intronic	1	0	0	PVS1_Strong,PM2,	LP

Gene	Transcript	Protein change	Variant type	Number of probands (this cohort)	HIC controls (FAF) n alelles = 10,508	gnomAD FAF popmax	ACMG rules	ACMG clasification
FLNC	NM_001458.4	c.3965-2A>T	Splicing	2	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
FLNC	NM_001458.4	c.4127+1delG	Splicing	1	0	0	PVS1_Strong,PM2,PP1,PS4_Supporting,	P
FLNC	NM_001458.4	c.4288+2T>G	Splicing	1	0	0	PVS1_Strong,PM2,PP1,PS4_Supporting,	P
FLNC	NM_001458.4	c.7251+1G>A	Splicing	1	0	0	PVS1_Strong,PM2,PP1_Moderate,PS4_Supporting,	P
FLNC	NM_001458.4	p.Arg 1474Glyfs*42	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
FLNC	NM_001458.4	p.Arg482*	Nonsense	1	0	0	PVS1_Strong,PM2,PP1_Moderate,PS4_Supporting,	P
FLNC	NM_001458.4	p.Gln2499*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
FLNC	NM_001458.4	p.Gly1800*	Nonsense	2	0	0	PVS1_Strong,PM2,PP1,PS4_Supporting,	P
FLNC	NM_001458.4	p.Gly201Valfs*36	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
FLNC	NM_001458.4	p.Gly2544Alafs*71	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
FLNC	NM_001458.4	p.His1205Thrfs*65	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
FLNC	NM_001458.4	p.Lys737Serfs*11	Frame-shift	2	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
FLNC	NM_001458.4	p.Phe1135Alafs*62	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
FLNC	NM_001458.4	p.Pro963Argfs*26	Frame-shift	1	0	0,00003	PVS1_Strong,PM2,PS4_Supporting,	P
FLNC	NM_001458.4	p.Trp744Argfs*4	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
FLNC	NM_001458.4	p.Tyr1840*	Nonsense	1	0	0	PVS1_Strong,PM2,PP1,	P
FLNC	NM_001458.4	p.Val2371Serfs*53	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
JPH2	NM_020433.4	p.Glu85Leu	Missense	1	0	0	PM2,PP1_Moderate,PP2,PP3,	LP
LMNA	NM_170707.3	c.1158-1G>A	Splicing	1	0	0	PVS1,PM2,PP1_Moderate,PP1,	P
LMNA	NM_170707.3	p.0?	codon	1	0	0	PVS1,PM2,PP1_Moderate,PP1,	P
LMNA	NM_170707.3	p.Ala318Glyfs*162	Frame-shift	1	0	0	PVS1,PM2,	LP
LMNA	NM_170707.3	p.Arg190Gln	Missense	1[#]	0	0	PP1_Strong,PM2,PS4_Moderate,PP1,PP2,PP3,PP5,	P
LMNA	NM_170707.3	p.Arg190Trp	Missense	3	0	0	PS4,PP1_Strong,PM2,PP1,PP2,PP3,PP5,	P
LMNA	NM_170707.3	p.Arg216Cys	Missense	1	0	0,00003	PM2,PS4_Moderate,PP1_Moderate,PP2,PP3,	LP
LMNA	NM_170707.3	p.Arg225*	Nonsense	2	0	0	PVS1,PS4,PP1_Strong,PM2,PP5,	P
LMNA	NM_170707.3	p.Arg321*	Nonsense	1	0	0	PVS1,PS4,PP1_Strong,PM2,PP5,	P
LMNA	NM_170707.3	p.Arg377Cys	Missense	1	0	0	PS4,PP1_Strong,PM2,PM5,PP3,PP5,	P
LMNA	NM_170707.3	p.Arg377His	Missense	2	0	0	PS4,PP1_Strong,PM2,PM5,PP3,PP5,	P
LMNA	NM_170707.3	p.Arg541Cys	Missense	1	0	0	PM2,PS4_Moderate,PP1,PP3,PP5,	LP
LMNA	NM_170707.3	p.Arg72Cys	Missense	1[#]	0	0	PM2,PS4_Moderate,PP1,PP3,PP4,PP5,	LP
LMNA	NM_170707.3	p.Glu105Lys	Missense	1	0	0	PM2,PP2,PP3,PP4,PS4_Supporting,	LP
LMNA	NM_170707.3	p.Glu124Lys	Missense	1	0	0	PM2,PP1_Moderate,PP2,PP3,PP4,PS4_Supporting,	LP
LMNA	NM_170707.3	p.Glu161Lys	Missense	1	0	0	PS4,PM2,PP1_Moderate,PP2,PP3,PP4,PP5,	LP

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LMNA	NM_170707.3	p.Glu444*	Nonsense	1	0	0	PVS1,PM2,	LP
LMNA	NM_170707.3	p.Gly382=	Splicing	1	0	0	PS3,PM2,PS4_Moderate,PP3,PP5,	LP
LMNA	NM_170707.3	p.Ser22*	Nonsense	2	0	0	PVS1,PM2,PS4_Supporting,	P
LMNA	NM_170707.3	p.Ser437HisFs*2	Frame-shift	1	0	0	PVS1,PM2,PP1_Moderate,PS4_Supporting,	P
LMNA	NM_170707.3	p.Thr27Ile	Missense	1	0	0	PM2,PS4_Moderate,PP1,PP2,PP4,PP5,	LP
LMNA	NM_170707.3	p.Trp514*	Nonsense	3	0	0	PVS1,PM2,PP1,PP5,PS4_Supporting,	P
LMNA	NM_170707.3	p.Tyr81Thrfs*15	Frame-shift	1	0	0	PVS1,PM2,PP1_Moderate,PP4,	P
MYBPC3	NM_000256.3	c.1224-19G>A	Inotronic	1	0	0,00019	PS3,PS4,PM2,PP1_Moderate,PP5,	P
MYBPC3	NM_000256.3	c.1226+1G>C	Splicing	1	0	0	PVS1,PM2,	LP
MYBPC3	NM_000256.3	c.2308+1G>A	Splicing	5	0	0	PVS1,PS4,PP1_Strong,PM2,	P
MYBPC3	NM_000256.3	c.407-1G>A	Splicing	1#	0	0,0001	PVS1,PM2,PS4_Supporting,	P
MYBPC3	NM_000256.3	p.Ala80delinsGlyGly	Inframe delins	1	0	0	PM2,PM4,PS4_Moderate,PP1,	LP
MYBPC3	NM_000256.3	p.Arg1271*	Nonsense	1	0	0,00003	PVS1,PM2,PS4_Moderate,PP5,	P
MYBPC3	NM_000256.3	p.Arg495Gly	Missense	1	0	0,00001	PS4,PP1_Strong,PM2,PP3,PP5,	P
MYBPC3	NM_000256.3	p.Arg820Trp	Missense	1	0	0,00003	PM2,PS4_Moderate,PP1_Moderate,PP3,	LP
MYBPC3	NM_000256.3	p.Arg891Alafs*160	Frame-shift	1	0	0	PVS1,PS4,PP1_Strong,PM2,PP5,	P
MYBPC3	NM_000256.3	p.Asp75Asn	Missense	1	2 (0,0002)	0,00004	PS4,PM2,PP1,PP3,	LP
MYBPC3	NM_000256.3	p.Glu1156*	Nonsense	1	0	0	PVS1,PM2,	LP
MYBPC3	NM_000256.3	p.Gly758=	Splicing	1#	0	0,00017	PS3,PM2,PP1,PS4_Supporting,	LP
MYBPC3	NM_000256.3	p.Gly868Ser	Splicing	1	1 (0,0001)	0,00029	PM2,PP3,PS4_Supporting,	LP
MYBPC3	NM_000256.3	sHisIleIle	Inframe delins	1	0	0	PM2,PM4,PM5,PS4_Supporting,	LP
MYBPC3	NM_000256.3	p.Lys505del	Inframe deletion	1	0	0,00003	PS4,PM2,PM4,	LP
MYH7	NM_000257.3	p.Arg1193Cys	Missense	1	0	0	PM5,PM2,PS4_Supporting,PP3	LP
MYH7	NM_000257.3	p.Arg1434Cys	Missense	1	0	0	PM2,PS4_Moderate,PP1,PP3	LP
MYH7	NM_000257.3	p.Arg1608His	Missense	2	0	0,00006	PM2,PS4_Supporting,PP1,PP3	LP
MYH7	NM_000257.3	p.Arg1781His	Missense	1#	1 (0,0001)	0,00007	PS4,PM2,PP1,PP5,	LP
MYH7	NM_000257.3	p.Arg243His	Missense	1	0	0,00003	PM2,PM1,PS4_Supporting,PP3	LP
MYH7	NM_000257.3	p.Arg453Cys	Missense	1	0	0	PS4,PS3,PM2,PP1_Moderate,PM1,PP3	LP
MYH7	NM_000257.3	p.Arg723Gly	Missense	1	0	0	PS4,PM5,PM2,PP1_Moderate,PM1,PP3	P
MYH7	NM_000257.3	p.Gln1381Pro	Missense	4	0	0	PM2,PS4_Supporting,PP1,PP3	LP
MYH7	NM_000257.3	p.Glu 883Lys	Missense	1	0	0	PM1,PM2,PM5,PP3,	LP
MYH7	NM_000257.3	p.Glu1426Lys	Missense	2	0	0	PM2,PS4_Moderate,PP1,PP3	LP
MYH7	NM_000257.3	p.Gly716Arg	Missense	2	0	0	PS4,PM2,PP1_Moderate,PM1,PP3	P

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MYH7	NM_000257.3	p.Ile457Met	Missense	1	0	0	PM5,PM2,PM1,PP3	LP
MYH7	NM_000257.3	p.Ile724Thr	Missense	1	0	0	PM2,PM1,PP1,PP3	P
MYH7	NM_000257.3	p.Phe252Leu	Missense	1	0	0	PM1,PM2,PM5,PP3,	LP
PKP2	NM_004572.3	c.1378+1G>A	Splicing	1#	0	0	PVS1,PM2,	LP
PKP2	NM_004572.3	p,Asp460Asn	Missense	1	0	0	PS4,PP1_Strong,PM2,PP3,PP5,	P
PKP2	NM_004572.3	p.Asn564Profs*53	Frame-shift	1	0	0	PVS1,PP1_Strong,PM2,PS4_Moderate,PP1,	P
PKP2	NM_004572.3	p.Glu259Glyfs*77	Frame-shift	2	1 (0,0001)	0	PVS1,PP1_Strong,PM2,PS4_Moderate,PP1,	P
PKP2	NM_004572.3	p.Ser329Argfs*23	Frame-shift	1#	0	0,00003	PVS1,PS4,PP1_Strong,PM2,PP1,PP5,	P
PLN	NM_002667.4	p.Arg14del	Inframe deletion	2	0	0,00002	PS3,PS4,PP1_Strong,PM2,PM4,PP5,	P
PRDM16	NM_022114.3	p.Val629Glyfs*5	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
RBM20	NM_001134363.2	c.1337+2T>A	Splicing	1	0	0	PVS1,PM2,PS4_Supporting,	LP
RBM20	NM_001134363.2	c.3317-16G>A	Splicing	2	0	0	PVS1,PM2,PS4_Supporting,	LP
RBM20	NM_001134363.2	c.3452-2A>G	Splicing	1	0	0	PVS1,PM2,	LP
RBM20	NM_001134363.2	Gln93Hisfs*11	Frame-shift	1	0	0	PVS1,PM2,	LP
RBM20	NM_001134363.2	p.Arg634Gln	Missense	1#	0	0,00004	PP1_Strong,PM2,PM5,PS4_Moderate,PP3,PP5,	P
RBM20	NM_001134363.2	p.Arg634Trp	Missense	8	0	0	PS3,PS4,PP1_Strong,PM2,PM5,PP3,PP5,	P
RBM20	NM_001134363.2	p.Arg636His	Missense	2	0	0	5,	P
RBM20	NM_001134363.2	p.Arg734Gly	Missense	1	0	0	PM1,PM2,PP2,PP3,	LP
RBM20	NM_001134363.2	p.Asp912Gly	Missense	2	0	0	PM1,PM2,PP1,PP3,PS4_Supporting,	LP
RBM20	NM_001134363.2	p.Pro638Leu	Missense	1	0	0	PP1_Strong,PM1,PM2,PS4_Moderate,PP3,PP5,	P
RBM20	NM_001134363.2	p.Ser175Alafs*10	Frame-shift	1	0	0	PVS1,PM2,	LP
RBM20	NM_001134363.2	p.Tyr594*	Nonsense	1#	0	0	PVS1,PM2,	LP
SGCD	NM_000337.5	p.Leu35Pro	Missense	1#	0	0	PM2,PM3,PP3,PP4,	LP
SGCD	NM_000337.5	p.Ser83*	Nonsense	1#	0	0	PVS1,PM2,PM3,PP4,	P
TBX20	NM_001077653.2	c.655-2A>G	Splicing	1	0	0	PVS1,PM2,	LP
TBX20	NM_001077653.2	p.Arg334*	Nonsense	1	0	0	PVS1,PM2,	LP
TBX20	NM_001077653.2	p.Gln407*	Nonsense	1	0	0	PVS1,PM2,	LP
TMEM43	NM_024334.2	p.Ser358Leu	Missense	1	0	0	PS3,PS4,PP1_Strong,PM2,PP3,PP5,	P
TNNC1	NM_003280.2	p.Glu134Lys	Missense	1	0	0	PM2,PM5,PM6,PP3,	LP
TNNI3	NM_000363.4	p.Ala157Val	Missense	1	0	0	PS3,PS4,PP1_Strong,PM2,PP2,PP3,	P
TNNI3	NM_000363.4	p.Glu67del	Inframe deletion	1	0	0	PM2,PM4,PP2,PS4_Supporting,	LP
TNNI3	NM_000363.4	p.Lys131del	Inframe deletion	1	0	0	PM2,PM4,PP2,PS4_Supporting,	LP

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TNNI3	NM_000363.4	p.Ser39Ilefs*2	Frame-shift	1	0	0,0001	PVS1,PM2,	LP
TNNT2	NM_001001430.2	p.Arg131Trp	Missense	2	0	0	PP2,PP3,PP5,	P
TNNT2	NM_001001430.2	p.Arg141Gln	Missense	2	0	0	PP2,PP3,PP5,	P
TNNT2	NM_001001430.2	p.Arg148Trp	Missense	1	0	0	PM1,PM2,PM5,PP1,PP2,PP3,	LP
TNNT2	NM_001001430.2	p.Arg159Gln	Missense	1	0	0	PM1,PM2,PP2,PP3,	LP
TNNT2	NM_001001430.2	p.Arg173Gln	Missense	2	0	0	PS3,PM1,PM2,PS4_Moderate,PP1,PP2,PP3,PP5,	P
TNNT2	NM_001001430.2	p.Arg173Gly	Missense	1	0	0	PM1,PM2,PM5,PP2,PP3,	LP
TNNT2	NM_001001430.2	p.Arg173Trp	Missense	1	0	0	PP2,PP3,	P
TNNT2	NM_001001430.2	p.Gly186Val	Missense	1	0	0	PM1,PM2,PP2,PP3,	LP
TNNT2	NM_001001430.2	p.Lys210del	Inframe deletion	1	0	0	PS3,PS4,PP1_Strong,PM2,PM4,PM6,PP2,PP3,PP5,	P
TNNT2	NM_001001430.2	p.Pro77Leu	Missense	2	1 (0,0001)	0,00017	PM2,PS4_Moderate,PP2,PP3,	LP
TPM1	NM_001018005.1	p.Asp230Asn	Missense	1	0	0	PS3,PP1_Strong,PM2,PS4_Moderate,PP2,PP3,PP5,	P
TPM1	NM_001018005.1	p.Leu113Val	Missense	2	0	0	PM2,PS4_Moderate,PP1,PP2,PP3,PP5,	P
TPM1	NM_001018005.1	p.Thr201Met	Missense	2	0	0	PM2,PS4_Moderate,PP2,PP3,	LP
TTN	NM_003319.4	c.17086+1G>A	Splicing	1	0	0,00003	PVS1_Strong,PM2,PP1,PS4_Supporting,	P
TTN	NM_003319.4	c.29453-1G>A	Splicing	2	0	0,00005	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	lGTAA	Splicing	2	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	c.32713+1G>A	Splicing	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	c.32731+1G>A	Splicing	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Ala12453Serfs*14	Frame-shift	1	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Ala19562Glufs*7	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Ala8464Profs*3	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg11576*	Nonsense	1	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Arg12420*	Nonsense	1	0	0,00002	PVS1_Strong,PM2,PP1,PS4_Supporting,	P
TTN	NM_003319.4	p.Arg12539*	Nonsense	1	0	0,00001	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg13434*	Nonsense	2	0	0,00002	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Arg14323*	Nonsense	1	0	0,00003	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Arg17482*	Nonsense	2	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg17658Valfs*11	Frame-shift	2	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg17691Serfs*2	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg18349*	Nonsense	1	0	0,00001	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Arg19299*	Nonsense	1	0	0,00003	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg19358*	Nonsense	1	0	0,00001	PVS1_Strong,PM2,PS4_Supporting,	P

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TTN	NM_003319.4	p.Arg19525*	Nonsense	1	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Arg19641*	Nonsense	1	0	0,00001	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg19714*	Nonsense	2	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Arg19949*	Nonsense	2	0	0,00001	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Arg20820*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg21708*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg23307Lysfs*9	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg23702Glyfs*26	Frame-shift	1	0	0,00001	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg2460*	Nonsense	1[#]	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg25493Thrfs*10	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg26587*	Nonsense	1	0	0,00002	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg3886Serfs*20	Frame-shift	1	0	0	PVS1_Strong,PM2,	P
TTN	NM_003319.4	p.Arg5014*	Nonsense	1	0	0,00001	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg5902*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg6833*	Nonsense	1	0	0,00001	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg7030*	Nonsense	2	0	0,00001	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Arg8256Glnfs*22	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Arg8272*	Nonsense	2	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Arg8276*	Nonsense	2[#]	0	0,00001	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Arg8676*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Asn15727Glnfs*29	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Asn4176*	Nonsense	2	0	0	PVS1_Strong,PM2,PS4_Moderate,	P
TTN	NM_003319.4	p.Asp13803Glufs*6	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Asp2143Thrfs*17	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Cys15522Argfs*8	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Gln11346*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Gln19243*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Gln26795*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Glu17490*	Nonsense	2	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Glu18482Lysfs*33	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Glu20947*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Glu21727Metfs*37	Frame-shift	1	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Glu3810*	Nonsense	1	0	0	PVS1_Strong,PM2,PS4_Supporting,	P

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TTN	NM_003319.4	p.Glu4090Argfs*7	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Glu7189Argfs*9	Frame-shift	1	1 (0,0001)	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Gly10458Serfs*5	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Gly14651Hisfs*6	Frame-shift	2	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Gly15350Glufs*26	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Gly6565*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.His24188Argfs*8	Frame-shift	1	0	0	PVS1_Strong,PM2,	P
TTN	NM_003319.4	p.His3553Glnfs*32	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.His8135Profs*13	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Ile18440Phefs*20	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Ile13887*	Nonsense	2	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Ile15632Asnfs*3	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Ile18440Phefs*20	Frame-shift	1	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Leu12514Valfs*12	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Leu13208Thrfs*24	Frame-shift	1	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Leu16652Glufs*6	Frame-shift	1	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Leu19964Serfs*12	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Leu5317Valfs*2	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Leu7907Glyfs*30	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Leu9263Hisfs*5	Frame-shift	1	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Lys11132Glyfs*2	Frame-shift	2	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Lys13943Asnfs*2	Frame-shift	1	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Lys16797Argfs*25	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Lys22926Glufs*12	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Lys2361Asnfs*10	Frame-shift	2	0	0	PVS1_Strong,PM2,PP1	P
TTN	NM_003319.4	p.Lys25446*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Lys26898Asnfs*9	Frame-shift	1[#]	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Lys4433Argfs*20	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Lys8000*	Nonsense	1	1 (0,0001)	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Met1529Serfs*6	Frame-shift	1	0	0,00001	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Phe19967Leufs*8	Frame-shift	2	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Pro10719Argfs*5	Frame-shift	1	0	0,00001	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Pro11634Glnfs*70	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP

Gene	Transcript	Protein change	Variant type	Number of probands (this cohort)	HIC controls (FAF) n alelles = 10,508	gnomAD FAF popmax	ACMG rules	ACMG clasification
TTN	NM_003319.4	p.Pro18608Glnfs*3	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Pro19320Leufs*4	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Ser13459Leufs*28	Frame-shift	1	0	0	PVS1_Strong,PM2,PP1	P
TTN	NM_003319.4	p.Ser13517Valfs*3	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Ser14999Argfs*13	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Ser15484*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Ser22260*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Ser22686Lysfs*5	Frame-shift	2	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Ser26322*	Nonsense	1[#]	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Ser6648Leufs*2	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Thr25963Trpfs*3	Frame-shift	2	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Trp12516Cysfs*16	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Trp13407*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Trp13432*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Trp14196*	Nonsense	1	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Trp15105*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Trp16080*	Nonsense	1[#]	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Trp17639*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Trp19433*	Nonsense	1	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Trp24348*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Trp5909*	Nonsense	1	0	0	PVS1_Strong,PM2,PP1	P
TTN	NM_003319.4	p.Trp7037*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Trp7111*	Nonsense	1[#]	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Trp7333*	Nonsense	1	0	0,00001	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Trp8041*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Tyr10450*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Tyr1346*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Tyr15839*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Tyr17457*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Tyr18140*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Tyr24298*	Nonsense	1	0	0,00001	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Tyr3186Cysfs*5	Frame-shift	1	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Tyr4119*	Nonsense	1	0	0	PVS1_Strong,PM2,PS4_Supporting,	P

Gene	Transcript	Protein change	Variant type	Number of probands (this cohort)	HIC controls (FAF) n alelles = 10,508	gnomAD FAF popmax	ACMG rules	ACMG clasification
TTN	NM_003319.4	p.Tyr9177*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Tyr9697*	Nonsense	1	0	0	PVS1_Strong,PM2,PS4_Supporting,	P
TTN	NM_003319.4	p.Tyr983*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Val12642Glyfs*19	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Val13475Trpfs*13	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Val16403Glufs*33	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Val23035Leufs*13	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Val24684*	Nonsense	1	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Val26578Alafs*5	Frame-shift	1[#]	0	0	PVS1_Strong,PM2,	LP
TTN	NM_003319.4	p.Val3023Tyrfs*23	Frame-shift	1	0	0	PVS1_Strong,PM2,	LP

[#] Variant identified in a patient with another P/LP variant (digenic or compound heterozygosis)

List of pathogenic and likely pathogenic variables identified in the validation cohort

Gene	Transcript	Protein change	Variant type	Number of probands (this cohort)	ACMG Pathogenicity	ACMG rules
ACTC1	NM_005159.4	p.Ile252Thr	Nonsynonymous	2	LP	PM2,PP1_Moderate,PP4,PS4_Supporting,
BAG3	NM_004281.3	p.Arg309*	Nonsense	2	P	PVS1,PM2,PS4_Moderate,PP1,PP5,
BAG3	NM_004281.3	p.Gln304*	Nonsense	2	P	PVS1,PM2,PP1,PP5,
CACNA1C	NM_199460.3	c.2914-1G>T	Splicing	1	LP	PVS1,PM2,
DES	NM_001927.3	p.Gly411Argfs*34	Frameshift	1	LP	PVS1,PM2,
DES	NM_001927.3	p.Gly437Valfs*10	Frameshift	1	LP	PVS1,PM2,
DMD	NM_004006.2	c.6118-3C>A	Splicing	1	LP	PVS1,PM2,
DMD	NM_004006.2	Del exons 48-49	CNVs	2	P	PVS1,PM2,PS4_Supporting,
DMD	NM_004006.2	Del exons 66-74	CNVs	1	P	PVS1,PM2,PS4_Supporting,
DMD	NM_004006.2	p.Trp3276*	Nonsense	1	P	PVS1,PM2,PP4,
DSC2	NM_024422.4	p.Ala800Leufs*56	Frameshift	2	LP	PVS1_Strong,PM2,
DSC2	NM_024422.4	p.Asp179Gly	Nonsynonymous	1	LP	PM2,PS4_Moderate,PP1,PP3,
DSC2	NM_024422.4	p.Gly8Argfs*23	Frameshift	1	LP	PVS1_Strong,PM2,
DSG2	NM_001943.5	p.Arg46Gln	Nonsynonymous	1	P	PS4,PM2,PM5,PP1_Moderate,PP3,
DSG2	NM_001943.5	p.Glu896Lysfs*8	Frameshift	1	LP	PVS1_Strong,PM2,
DSP	NM_004415.3	p.Arg1934*	Nonsense	1	P	PVS1,PM2,PP1,PS4_Supporting,
DSP	NM_004415.3	p.Arg2160*	Nonsense	1	P	PVS1,PM2,PS4_Supporting,
DSP	NM_004415.3	p.Gln1262*	Nonsense	2	P	PVS1,PM2,PS4_Supporting,
DSP	NM_004415.3	p.Gln631*	Nonsense	1	LP	PVS1,PM2,
DSP	NM_004415.3	p.Gly2133Valfs*2	Frameshift	1	LP	PVS1,PM2,
DSP	NM_004415.3	p.Ile120Asnfs*16	Frameshift	1	LP	PVS1,PM2,
DSP	NM_004415.3	p.Ile2631Asnfs*13	Frameshift	1	LP	PVS1,PM2,
DSP	NM_004415.3	p.Ser2591Argfs*11	Frameshift	2	P	PVS1,PM2,PS4_Supporting,
DSP	NM_004415.3	p.Val1128Glyfs*5	Frameshift	1	P	PVS1,PM2,PS4_Supporting,
EMD	NM_000117.2	p.Lys37del	Inframe deletion	1	LP	PM2,PP1_Moderate,PP4,PS4_Supporting,
FLNC	NM_001458.4	c.3791-1G>A	Splicing	6	P	PVS1_Strong,PM2,PS4_Moderate,
FLNC	NM_001458.4	c.5842+2T>A	Splicing	2	P	PVS1_Strong,PM2,PS4_Supporting,
FLNC	NM_001458.4	c.7251+1G>A	Splicing	1	P	PVS1_Strong,PM2,PP1_Moderate,PS4_Supporting,
FLNC	NM_001458.4	c.7252-2A>G	Splicing	1	LP	PVS1_Strong,PM2,
FLNC	NM_001458.4	p.Arg1370*	Nonsense	1	LP	PVS1_Strong,PM2,
FLNC	NM_001458.4	p.Arg2326*	Nonsense	1	P	PM2,PP1_Moderate,PP4,PS4_Supporting,
FLNC	NM_001458.4	p.Arg269*	Nonsense	1	P	PM2,PP1_Moderate,PP4,PS4_Supporting,
FLNC	NM_001458.4	p.Asp2703Trpfs	Frameshift	1	LP	PM2,PM4,PP1,PS4_Supporting,
FLNC	NM_001458.4	p.Gln1956*	Nonsense	1	LP	PVS1_Strong,PM2,

Gene	Transcript	Protein change	Variant type	Number of probands (this cohort)	ACMG Pathogenicity	ACMG rules
FLNC	NM_001458.4	p.Glu151*	Nonsense	1	LP	PVS1_Strong,PM2,
FLNC	NM_001458.4	p.Gly2070Ser	Nonsynonymous	1	LP	PM2,PP3,PP4,PP5,PS4_Supporting,
FLNC	NM_001458.4	p.Pro2081Leufs*2	Frameshift	1	LP	PVS1_Strong,PM2,
FLNC	NM_001458.4	p.Pro2081Lfs*2	Frameshift	2	LP	PVS1_Strong,PM2,
FLNC	NM_001458.4	p.Pro2298fs	Frameshift	1	LP	PVS1_Strong,PM2,
FLNC	NM_001458.4	p.Ser1985*	Nonsense	1	LP	PVS1_Strong,PM2,PS4_Supporting,
FLNC	NM_001458.4	p.Tyr2381Glyfs	Frameshift	1	P	PVS1_Strong,PM2,PP1_Moderate,PS4_Supporting,
FLNC	NM_001458.4	p.Val2290Argfs*23	Frameshift	3	P	PVS1_Strong,PM2,PS4_Supporting,
GLA		p.Phe113Leu	Nonsynonymous	1	P	PS3,PS4,PM2,PP3,PP4,
LMNA	NM_170707.3	c.1608+1G>T	Splicing	1	P	PVS1,PM2,PP4,PS4_Supporting,
LMNA	NM_170707.3	c.357-2A>G	Splicing	1	P	PVS1,PM2,PS4_Supporting,
LMNA	NM_170707.3	p.Arg190Gln	Nonsynonymous	1	P	PP1_Strong,PM2,PS4_Moderate,PP1,PP2,PP3,PP5,
LMNA	NM_170707.3	p.Arg190Trp	Nonsynonymous	3	P	PS4,PP1_Strong,PM2,PP1,PP2,PP3,PP5,
LMNA	NM_170707.3	p.Arg216Cys	Nonsynonymous	1	P	PM2,PS4_Moderate,PP1_Moderate,PP2,PP3,PP4,
LMNA	NM_170707.3	p.Arg321Glufs*159	Frameshift	1	P	PVS1,PM2,PP4,
LMNA	NM_170707.3	p.Arg331Gln	Nonsynonymous	1	LP	PM2,PS4_Moderate,PP2,PP3,PP4,
LMNA	NM_170707.3	p.Arg377Leu	Nonsynonymous	1	P	PM2,PM5,PS4_Moderate,PP2,PP3,PP4,
LMNA	NM_170707.3	p.Arg89Leu	Nonsynonymous	1	LP	PM2,PS4_Moderate,PP1,PP2,PP3,PP4,
LMNA	NM_170707.3	p.Asn195Tyr	Nonsynonymous	1	LP	PM2,PM5,PP2,PP3,PP4,
LMNA	NM_170707.3	p.Glu105Leu	Nonsynonymous	3	LP	PM2,PP2,PP3,PP4,PS4_Supporting,
LMNA	NM_170707.3	p.Glu161Lys	Nonsynonymous	5	P	PS4,PM2,PP1_Moderate,PP2,PP3,PP4,PP5,
LMNA	NM_170707.3	p.Glu317Lys	Nonsynonymous	1	P	PS4,PM1,PM2,PP1_Moderate,PP2,PP3,PP4,
LMNA	NM_170707.3	p.Glu347Lys	Nonsynonymous	1	LP	PS4,PM2,PS4_Moderate,PP2,PP3,PP4,
LMNA	NM_170707.3	p.Gly382=	Splicing	2	LP	PS3,PM2,PS4_Moderate,PP3,PP5,
LMNA	NM_170707.3	p.Val70Serfs*25	Frameshift	1	P	PVS1,PM2,PP1,PP4,
MyBPC3	NM_000256.3	p.Arg1022Pro	Nonsynonymous	1	P	PS4,PM2,PM5,PP1_Moderate,PP3,
MyBPC3	NM_000256.3	p.Cys566Arg	Nonsynonymous	1	LP	PM2,PP1_Moderate,PP3,PS4_Supporting,
MyBPC3	NM_000256.3	p.Trp792Valfs*41	Frameshift	1	P	PVS1,PS4,PM2,PP1_Moderate,
MYH7	NM_000257.3	c.732+1G>A	Splicing	1	LP	PVS1_Moderate,PM2,PS4_Moderate,PP1_Moderate,PM1,
MYH7	NM_000257.3	p.Arg1434Cys	Nonsynonymous	1	LP	PM2,PS4_Moderate,PP1,PP3
MYH7	NM_000257.3	p.Arg1500Trp	Nonsynonymous	1	LP	PM5,PM2,PS4_Supporting,PP1,PP3
MYH7	NM_000257.3	p.Arg237Trp	Nonsynonymous	1	LP	PM2,PM1,PS4_Supporting,PP3
MYH7	NM_000257.3	p.Arg403Trp	Nonsynonymous	2	P	PS4,PS3,PM2,PP1_Moderate,PP3
MYH7	NM_000257.3	p.Arg723Cys	Nonsynonymous	1	P	PS4,PM5,PM2,PP1_Moderate,PM1,PP3

Gene	Transcript	Protein change	Variant type	Number of probands (this cohort)	ACMG Pathogenicity	ACMG rules
MYH7	NM_000257.3	p.Arg904His	Nonsynonymous	1	LP	PM5,PM2,PM1,PS4_Supporting,PP3
MYH7	NM_000257.3	p.Glu1286Lys	Nonsynonymous	1	LP	PM2,PP2,PP3,PP5,PS4_Supporting,
MYH7	NM_000257.3	p.Glu1426Lys	Nonsynonymous	1	LP	PM2,PS4_Moderate,PP1,PP3
MYH7	NM_000257.3	p.Glu1801Lys	Nonsynonymous	1	LP	PM2,PS4_Moderate,PP1,PP3
MYH7	NM_000257.3	p.Gly1057Ser	Nonsynonymous	1	LP	PM2,PP1,PP2,PP3,PS4_Supporting,
MYH7	NM_000257.3	p.Gly733Arg	Nonsynonymous	1	LP	PM1,PM2,PP2,PP3,
PKP2	NM_004572.3	p.Lys672Argfs*12	Frameshift	1	P	PVS1,PS4,PM2,PP1,
PKP2	NM_004572.3	Whole gene deletion	CNVs	1	P	PVS1,PM2,PS4_Supporting,
PLN	NM_002667.4	p.Arg14del	Inframe deletion	2	P	PS3,PS4,PP1_Strong,PM2,PM4,PP5,
PRDM16	NM_022114.3	2603+2T>C	Splicing	1	LP	PVS1_Strong,PM2,
RBM20	NM_001134363.2	p.Arg634Trp	Nonsynonymous	2	P	PS3,PS4,PP1_Strong,PM2,PM5,PP3,PP5,
RBM20	NM_001134363.2	p.Arg636His	Nonsynonymous	3	P	PP1_Strong,PM1,PM2,PM5,PS4_Moderate,PP3,PP5,
RBM20	NM_001134363.2	p.Arg688*	Nonsense	1	LP	PVS1_Strong,PM2,
RBM20	NM_001134363.2	p.Pro140Argfs*3	Frameshift	1	LP	PVS1_Strong,PM2,
SCN5A	NM_198056.2	p.Ala204Val	Nonsynonymous	1	LP	PM2,PP2,PP3,PP4,PS4_Supporting,
SCN5A	NM_198056.2	p.Arg222Gln	Nonsynonymous	2	P	PS3,PS4,PM2,PP1_Moderate,PP3,
SCN5A	NM_198056.2	p.Gly752Arg	Nonsynonymous	1	P	PS3,PM2,PP1,PP2,PP3,PS4_Supporting,
SCN5A	NM_198056.2	p.Val1353Met	Nonsynonymous	1	LP	PM1,PM2,PP3,PS4_Supporting,
TNNC1	NM_003280.2	p.Asn144Asp	Nonsynonymous	1	LP	PM2,PM5,PM6,PP3,
TNNT2	NM_001001430.2	p.Arg139His	Nonsynonymous	1	LP	PM1,PM2,PM5,PP1,PP3,PS4_Supporting,
TNNT2	NM_001001430.2	p.Arg141Gln	Nonsynonymous	1	P	PM1,PM2,PM5,PP1,PP3,PS4_Supporting,
TNNT2	NM_001001430.2	p.Arg148Trp	Nonsynonymous	1	LP	PM1,PM2,PP1,PP3,PS4_Supporting,
TNNT2	NM_001001430.2	p.Arg173Trp	Nonsynonymous	12	P	PS3,PM1,PM2,PM5,PS4_Moderate,PP1_Moderate,PP2,PP3,
TNNT2	NM_001001430.2	p.Arg196Gln	Nonsynonymous	6	LP	PM1,PM2,PM5,PP3,PS4_Supporting,
TNNT2	NM_001001430.2	p.Glu161Lys	Nonsynonymous	1	LP	PM1,PM2,PP2,PP3,
TNNT2	NM_001001430.2	p.Lys207Ilefs*13	Frameshift	2	LP	PVS1_Strong,PM2,PS4_Supporting,
TPM1	NM_001018005.1	p.Asp84Asn	Nonsynonymous	1	LP	PM2,PP1,PP2,PP3,PS4_Supporting,
TPM1	NM_001018005.1	p.Glu62Gln	Nonsynonymous	2	LP	PM2,PP1,PP2,PP3,PS4_Supporting,
TPM1	NM_001018005.1	p.Val95Ala	Nonsynonymous	1	LP	PM2,PP1_Moderate,PP2,PP3,PS4_Supporting,
TTN	NM_003319.4	c.13282+1G>A	Splicing	2	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	c.14414-2A>C	Splicing	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	c.19501+2T>C	Splicing	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	c.25808-1G>A	Splicing	2	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	c.28074+3A>G	Splicing	1	LP	PVS1_Strong,PM2,

Gene	Transcript	Protein change	Variant type	Number of probands (this cohort)	ACMG Pathogenicity	ACMG rules
TTN	NM_003319.4	c.30652+4delGTAA	Splicing	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	c.32731+1G>A	Splicing	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	c.36599-1G>A	Splicing	3	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p. Gln25869*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p. Ser22759*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p. Trp2694*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Ala10378Leufs*2	Frameshift	2	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Ala10766Glufs*3	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Ala13034Valfs*13	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Ala3951fs*5	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg10046*	Nonsense	4	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg11246*	Nonsense	2	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Arg11576*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg12602*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg13434*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg14803*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg17063Trpfs*2	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg18444*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg18741Serfs*23	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg19299*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg19338*	Nonsense	3	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Arg19949*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg2037Lysfs*56	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg21991*	Nonsense	3	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Arg22190*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg22605*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg25469Asnfs*19	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg25633Glufs*48	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg4816*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg7701*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Arg9075*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Asn18373Lysfs*2	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Asn22924Thrfs*2	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Asn7364Lysfs*6	Frameshift	1	LP	PVS1_Strong,PM2,

Gene	Transcript	Protein change	Variant type	Number of probands (this cohort)	ACMG Pathogenicity	ACMG rules
TTN	NM_003319.4	p.Asp16692Argfs*25	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Asp4927Phefs*7	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Asp5025Ilefs*2	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Asp7627Argfs*25	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Cys15379*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Gln13145*	Nonsense	2	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Gln15012Valfs*11	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Gln15459fs*3	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Gln16775*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Gln20329*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Gln26533*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Gln3743*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Glu13429*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Glu18447fs*12	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Glu19857*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Glu21059*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Glu8326*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Glu9990*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Gly13222*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Gly14825*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Gly19620Trpfs*10	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Gly21352Valfs*44	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Gly7071fs*10	Frameshift	1	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Gly7071fs*10	Frameshift	1	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Gly8908Glufs*18	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Ile12461Lysfs*4	Frameshift	3	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Ile9380Leufs*42	Frameshift	4	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Lys11878Argfs*9	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Lys14986Asnfs*30	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Lys17360*4*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Lys20040*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Lys22383Asnfs*8	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Lys23675Argfs*16	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Lys24341Argfs*13	Frameshift	1	LP	PVS1_Strong,PM2,

Gene	Transcript	Protein change	Variant type	Number of probands (this cohort)	ACMG Pathogenicity	ACMG rules
TTN	NM_003319.4	p.Lys4004Argfs*27	Frameshift	7	P	PVS1_Strong,PM2,PS4_Moderate,
TTN	NM_003319.4	p.Met14564fs*36	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Phe24969Leufs*23	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Pro12498Leufs*10	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Pro13491Leufs*19	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Pro13683Hisfs*15	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Pro19096Cysfs*17	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Pro20196Glnfs*10	Frameshift	4	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Ser12942Cysfs*18	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Ser14150Argfs*19	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Ser19741Valfs*	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Ser20089Lysfs*3	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Ser21018Argfs*29	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Ser3833*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Ser6648Leufs*2	Frameshift	4	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Ser9193Valfs*34	Frameshift	2	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Thr23412Asnfs*13	Frameshift	2	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Thr3797Profs*8	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Trp14196*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Thr14749Asnfs*13	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Trp21894*	Nonsense	3	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Trp25105*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Trp5998*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Tyr13061*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Tyr16702Leufs*4	Frameshift	2	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Tyr22496*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Val17902Tyrfs*16	Frameshift	3	P	PVS1_Strong,PM2,PS4_Supporting,
TTN	NM_003319.4	p.Val21702*	Nonsense	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Val22025Glnfs*5	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Val22853Glnfs*10	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Val7540Phefs*24	Frameshift	1	LP	PVS1_Strong,PM2,
TTN	NM_003319.4	p.Met6522Asnfs*4	Frameshift	1	LP	PVS1_Strong,PM2,