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Supplementary Material

A Case Series of Hypertrophic Cardiomyopathy Conducted in Vietnam Revealing a Novel Pathogenic Variant of the TNNT2 Gene

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Table S1. For novel pathogenic variant on TNNT2 - PATHOGENIC.

Rule	Pathogenicity	Explanation
PVS1	Pathogenic Very Strong	Null variant (within ±2 of splice site) affecting gene TNNT2, which is a known mechanism of disease (gene has 61 known pathogenic variants which is greater than minimum of 5), associated with Cardiomyopathy, familial restrictive, 3, Cardiomyopathy, dilated, 1D, Left ventricular noncompaction 6 and Cardiomyopathy, familial hypertrophic, 2 .
PM2	Pathogenic Moderate	Variant not found in GnomAD exomes (good GnomAD exomes coverage = 66.6). Variant not found in GnomAD genomes (good GnomAD genomes coverage = 32.2).
PP3	Pathogenic Supporting	Pathogenic computational verdict because 4 pathogenic predictions from DANN, EIGEN, FATHMM-MKL and MutationTaster vs no benign predictions.

Table S2. For variant p.R783H on MYH7 – LIKELY PATHOGENIC.

Rule	Pathogenicity	Explanation
PM1	Pathogenic Moderate	Hot-spot of length 61 base-pairs has 17 non-VUS variants (13 pathogenic and 4 benign) , pathogenicity = 76.5% which is more than threshold 51.0%.
PM2	Pathogenic Moderate	GnomAD exomes allele frequency = 0.0000159 is less than 0.0001 threshold for recessive gene MYH7 (good GnomAD exomes coverage = 89.6). GnomAD genomes allele frequency = 0.0000637 is less than 0.0001 threshold for recessive gene MYH7 (good GnomAD genomes coverage = 32.0).
PM5	Pathogenic Moderate	Alternative variant chr14:23894566 C => G (Arg783Pro) is is classified Likely Pathogenic, one star, by ClinVar (confirmed using ACMG). Alternative variant chr14:23894567 G => A (Arg783Cys) is is classified Pathogenic, one star, by ClinVar (confirmed using ACMG). Alternative variant chr14:23894567 G => C (Arg783Gly) is is classified Likely Pathogenic, one star, by ClinVar (confirmed using ACMG).

PP2	Pathogenic Supporting	395 out of 408 non-VUS missense variants in gene MYH7 are pathogenic = 96.8% which is more than threshold of 51.0%, and 425 out of 1,333 clinically reported variants in gene MYH7 are pathogenic = 31.9% which is more than threshold of 12.0%.
BP4	Benign Supporting	Benign computational verdict because 6 benign predictions from DEOGEN2, FATHMM-MKL, MutationAssessor, MutationTaster, PrimateAI and SIFT vs 5 pathogenic predictions from DANN, EIGEN, M-CAP, MVP and REVEL and the position is not conserved (GERP++ rejected substitutions = 4.6 is less than 6.8).

Table S3. For variant p.T1377M on MYH7 - PATHOGENIC.

Rule	Pathogenicity	Explanation
PM2	Pathogenic Moderate	GnomAD exomes allele frequency = 0.00000398 is less than 0.0001 threshold for recessive gene MYH7 (good GnomAD exomes coverage = 98.2). Variant not found in GnomAD genomes (good GnomAD genomes coverage = 32.0).
PP2	Pathogenic Supporting	395 out of 408 non-VUS missense variants in gene MYH7 are pathogenic = 96.8% which is more than threshold of 51.0%, and 425 out of 1,333 clinically reported variants in gene MYH7 are pathogenic = 31.9% which is more than threshold of 12.0%.
PP3	Pathogenic Supporting	Pathogenic computational verdict because 11 pathogenic predictions from DANN, DEOGEN2, EIGEN, FATHMM-MKL, M-CAP, MVP, MutationAssessor, MutationTaster, PrimateAI, REVEL and SIFT vs no benign predictions.
PP5	Pathogenic Very Strong	Using strength Very Strong because ClinVar classifies this variant as Likely Pathogenic, rated three stars, reviewed by expert panel. UniProt classifies this variant as 'disease' (Cardiomyopathy, Familial Hypertrophic 1).

Table S4. For variant p.R1114H on MYH7 – LIKELY PATHOGENIC.

Rule	Pathogenicity	Explanation
PM2	Pathogenic Moderate	GnomAD exomes allele frequency = 0.0000123 is less than 0.0001 threshold for recessive gene MYH7 (good GnomAD exomes coverage = 68.3). Variant not found in GnomAD genomes (good GnomAD genomes coverage = 30.6).
PP2	Pathogenic Supporting	395 out of 408 non-VUS missense variants in gene MYH7 are pathogenic = 96.8% which is more than threshold of 51.0%, and 425 out of 1,333 clinically reported variants in gene MYH7 are pathogenic = 31.9% which is more than threshold of 12.0%.
PP3	Pathogenic Supporting	Pathogenic computational verdict because 11 pathogenic predictions from DANN, DEOGEN2, EIGEN, FATHMM-MKL, M-CAP, MVP, MutationAssessor, MutationTaster, PrimateAI, REVEL and SIFT vs no benign predictions.
PP5	Pathogenic Supporting	ClinVar classifies this variant as Likely Pathogenic, rated one star, .

Table S5. For variant p.R1114H on MYH7 – LIKELY PATHOGENIC.

Rule	Pathogenicity	Explanation
PM1	Pathogenic Moderate	Hot-spot of length 61 base-pairs has 11 non-VUS variants (6 pathogenic and 5 benign) , pathogenicity = 54.5% which is more than threshold 51.0%.
PM2	Pathogenic Moderate	GnomAD exomes allele frequency = 0.0000161 is less than 0.0001 threshold for recessive gene MYBPC3 (good GnomAD exomes coverage = 53.8). Variant not found in GnomAD genomes (good GnomAD genomes coverage = 33.6).
PP2	Pathogenic Supporting	114 out of 149 non-VUS missense variants in gene MYBPC3 are pathogenic = 76.5% which is more than threshold of 51.0%, and 563 out of 1,197 clinically reported variants in gene MYBPC3 are pathogenic = 47.0% which is more than threshold of 12.0%.
PP3	Pathogenic Supporting	Pathogenic computational verdict because 9 pathogenic predictions from DANN, DEOGEN2, EIGEN, FATHMM-MKL, M-CAP, MutationAssessor, MutationTaster, PrimateAI and SIFT vs no benign predictions.
PP5	Pathogenic Moderate	Using strength Moderate because ClinVar classifies this variant as Pathogenic, rated two stars, multiple submissions with no conflicts. UniProt classifies this variant as 'disease' (Cardiomyopathy, Familial Hypertrophic 4).

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