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ORIGINAL RESEARCH

Genotype and Cardiac Outcomes in Pediatric Dilated Cardiomyopathy

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BACKGROUND: Pediatric dilated cardiomyopathy (DCM) is a well-known clinical entity; however, phenotype–genotype correlations are inadequately described. Our objective was to provide genotype associations with life-threatening cardiac outcomes in pediatric DCM probands.

METHODS AND RESULTS: We performed a retrospective review of children with DCM at a large pediatric referral center (2007–2016), excluding syndromic, chemotherapy-induced, and congenital heart disease causes. Genetic variants were adjudicated by an expert panel and an independent clinical laboratory. In a cohort of 109 pediatric DCM cases with a mean age at diagnosis of 4.2 years (SD 5.9), life-threatening cardiac outcomes occurred in 47% (42% heart transplant, 5% death). One or more pathogenic/likely pathogenic variants were present in 40/109 (37%), and 36/44 (82%) of pathogenic/likely pathogenic variants occurred in sarcomeric genes. The frequency of pathogenic/likely pathogenic variants was not different in patients with familial cardiomyopathy (15/33 with family history versus 25/76 with no family history, P=0.21). *TTN* truncating variants occurred in a higher percentage of children diagnosed as teenagers (26% teenagers versus 6% younger children, P=0.01), but life-threatening cardiac outcomes occurred in both infants and teenagers with these *TTN* variants. DCM with left ventricular noncompaction features occurred in 6/6 patients with *MYH7* variants between amino acids 1 and 600.

CONCLUSIONS: Sarcomeric variants were common in pediatric DCM. We demonstrated genotype-specific associations with age of diagnosis and cardiac outcomes. In particular, *MYH7* had domain-specific association with DCM with left ventricular noncompaction features. Family history did not predict pathogenic/likely pathogenic variants, reinforcing that genetic testing should be considered in all children with idiopathic DCM.

Key Words: dilated cardiomyopathy ■ genotype ■ pediatrics ■ transplant

Dilated cardiomyopathy (DCM) is a heart muscle disease characterized by ventricular dilation associated with systolic dysfunction.[1] Between one third and one half of children with DCM progress to heart failure, death, or transplantation within 2 years of diagnosis. DCM is the indication for 45% of heart transplants in the pediatric population, primarily associated with chronic symptomatic heart failure.[2] Sudden death has an annual incidence of 2% to 3% in pediatric patients with DCM.[3,4]

Between 25% and 50% of DCM cases are familial, underscoring the importance of genetic contribution.[5,6] The pathogenesis of genetically mediated DCM has been associated with genes that encode sarcomeric proteins, components of the cytoskeleton, nuclear envelope proteins, and ion channels.[7] Even among DCM associated with nongenetic causes such as hypertension, valve disease, inflammatory/infectious causes, and toxins, genetic background may influence clinical phenotype and outcome.[5]

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CLINICAL PERSPECTIVE

What Is New?

- Life-threatening cardiac outcomes occurred in approximately half of patients with pediatric dilated cardiomyopathy.
- Pathogenic/likely pathogenic variants occurred in one third of patients and there was a high prevalence of variants in sarcomeric genes (>80%).
- Dilated cardiomyopathy in the setting of *TTN* truncating variants was associated with life-threatening cardiac outcomes in infants and older children.

What Are the Clinical Implications?

- Family history did not predict pathogenic/likely pathogenic variants, reinforcing that genetic testing should be considered in all children with idiopathic dilated cardiomyopathy.
- *TTN* truncating variants were associated with severe outcomes at all ages and should be considered as potentially pathogenic even in infants and young children.

Nonstandard Abbreviations and Acronyms

DCM	dilated cardiomyopathy
M-LVNC	dilated cardiomyopathy with left ventricular noncompaction features
P/LP	pathogenic/likely pathogenic
VUS	variants of uncertain significance

Genetic Variation Linked to Age of Onset and Clinical Course

For certain genes, age of onset and genetic DCM have been associated. For example, some *RAF-1* variants have been associated with childhood-onset DCM.[8] In Becker muscular dystrophy, region-specific dystrophin deletions are associated with earlier onset of cardiomyopathy.[9] Adults with nonsense mutations in the *BAG3* gene had early-onset DCM with arrhythmias.[10] In addition, there is evidence that some genetic variants predict disease severity. *LMNA* variants in DCM can present with conduction system abnormalities and arrhythmia before ventricular dilation.[11] Adult studies have also demonstrated that patients with *LMNA* variants have high rates of heart transplantation and those with *RBM20* variants were transplanted at a younger age.[12] Specific variants in *PLN* and *TPM1* have also been identified as particularly severe in certain populations.[13,14]

Clinical Implications in Children

Although studies have examined outcomes of genetic testing in adults with DCM, there is a paucity of data on the yield, mutations, and clinical correlates with genetic testing in the pediatric DCM population. To address this, we collected information on children who presented with DCM and had undergone clinical genetic testing using gene panels.

METHODS

We performed a retrospective review of patients with DCM at a single tertiary pediatric referral center. Cases were included if they presented in the inpatient or outpatient setting from 2007 to 2016, received a clinical evaluation by a cardiomyopathy specialist, and had at least 1 commercial genetic panel that included cardiomyopathy genes (Table S1). The Institutional Review Board at Ann & Robert H. Lurie Children's Hospital provided human subjects protection. The data that support the findings of this study are available in the Supplemental Material or can be obtained from the corresponding author upon reasonable request.

Inclusion and Exclusion Criteria

Clinical inclusion was determined using echocardiographic criteria for DCM established by the PCMR (Pediatric Cardiomyopathy Registry).[15] These criteria require 1 or more of the following: (1) left ventricular fractional shortening or ejection fraction (EF) >2 SDs below the normal mean for age, (2) end systolic left ventricular posterior wall thickness >2 SDs below the normal mean for body-surface area, or (3) left ventricular end-diastolic dimension or volume >2 SDs above the normal mean for body-surface area. Three patients with DCM received a heart transplant elsewhere and detailed echocardiographic measurements from the explanted heart were not available for review.

Clinical exclusion criteria included having a known genetic syndrome with definitive extracardiac manifestations including neuromuscular disease; a complex congenital heart defect leading to ventricular dysfunction; significant iatrogenic exposures associated with the development of cardiomyopathy (eg, anthracycline therapy); or a minimal genetic evaluation (eg, specific testing for only 1 gene rather than a panel approach). To minimize selection bias, we included patients with a diagnosis of myocarditis if they also met the primary PCMR inclusion criteria.

Data Collection

Study data were collected and managed using REDCap (Research Electronic Data Capture) hosted at Northwestern University Clinical and Translational

Sciences Institute.[16] Baseline information included demographics, presentation data (age at diagnosis, length of stay, and presence of significant arrhythmias), family history data, and cardiac diagnostic data. Report of race was obtained by retrospective chart review and classified according to the nomenclature available in our electronic medical record. The primary outcome measure was a life-threatening cardiac outcome, defined as 1 or more of the following: resuscitated cardiac arrest, mechanical circulatory support, heart transplant, or death secondary to a cardiac cause.

All available data in the echocardiographic database were reviewed and data from the echocardiogram with the lowest EF (or fractional shortening if EF was not available) were used for primary analysis. Mitral regurgitation was based on a 7-point ordinal scale ranging from "Absent" to "Severe," based on the echocardiographer's written interpretation. Unclear interpretations were evaluated by direct image review. Rhythm abnormalities were tabulated exclusively from pretransplant hearts and included sustained atrial, junctional, or ventricular arrhythmias or nonsustained ventricular arrhythmias (≥4 beats).

A patient was classified with familial cardiomyopathy if any relative(s) had cardiomyopathy. The subgroup with familial cardiomyopathy was divided into those who had first-degree relatives with cardiomyopathy and those with only higher-degree relatives with cardiomyopathy.

During the study dates, the following commercial panels were used: the Pan Cardiomyopathy Panel and the DCM Panels A/B by Laboratory for Molecular Medicine (Harvard Partners), the Comprehensive Cardiomyopathy Panel and the Combined Cardiac Panel (GeneDx), and the Familion DCM Test (Transgenomic).

Variant Classification

All variants were clinically adjudicated using American College of Medical Genetics Standards and Guidelines interpreted by a committee of adult and pediatric cardiomyopathy and arrhythmia practitioners, and a genetic counselor with expertise in cardiomyopathy (authors R.K., E.M, E.P., L.D-C., and G.W.), all blinded to the identity of the patients, but aware of the clinical phenotype and variant segregation within the family. This clinical adjudication was used for the primary analysis. *ACTN2, MYBPC3, MYH7, MYL2, TNNC1, TNNT2, TPM1,* and *TTN* were classified as genes encoding sarcomeric proteins. Missense variants in *TTN* were excluded from analysis. To minimize potential classification bias, we also submitted all variants for independent classification in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory according to the American College of Medical Genetics Standards and Guidelines.[17] The independent laboratory received the standard phenotype details that would be available during clinical variant analysis. The classification from the original report at the time of patient care and both reclassifications are tabulated in Table S2.

Statistical Analysis

Chi-squared or Fisher exact analyses (Stata 15.1, College Station, TX) were used to compare categorical variables, including univariate analysis of variant pathogenicity and clinical/demographic features. A Spearman correlation coefficient was used to assess mitral regurgitation against continuous variables and a Student *t* test was used for left ventricular end diastolic *Z*-scores, EF, and age at presentation. A value of $P<0.05$ was accepted as statistically significant. The clinical variant adjudication was used for analysis; however, analyses were repeated using the independent classification from the independent laboratory to ensure that the classification schema did not change the statistical significance.

RESULTS

Patient Characteristics

We identified 299 children with DCM from January 1, 2007 to December 31, 2016, without syndromic features, congenital heart disease, or chemotherapy exposure. Of those, 109 of 299 (36%) were tested with a cardiomyopathy genetic panel. Patients who received a genetic panel had a more severe clinical presentation, with a lower mean left ventricular EF at diagnosis (29.4% versus 50.1%, $P<0.001$) and a lower EF on their most severely depressed echocardiogram (24.1% versus 39.9%, $P<0.001$), when compared with nongenotyped patients.

Among the 109 genotyped patients retained for further analysis, the mean age at diagnosis was 4.2 years (±5.9), with a range of 0 to 17.6 years. Life-threatening cardiac outcomes (resuscitated cardiac arrest, mechanical circulatory support, heart transplant, or death) occurred in 51 patients (47%), of whom 46 underwent heart transplant. Figure 1 shows the time from diagnosis to the first life-threatening cardiac outcome. Two patients died without having undergone heart transplant and 6 died after heart transplant.

A more concise end point of death or transplant was also considered. Death or transplant occurred in 48/51 patients with a life-threatening cardiac outcome. The other 3 patients had a cardiac arrest or sustained ventricular tachycardia with syncope. A sensitivity analysis for the population with only death or transplant was unchanged with respect to genotype prevalence.

Table tabulates clinical and echocardiographic data. There was no meaningful latency between presentation with symptoms and initial imaging diagnosis.

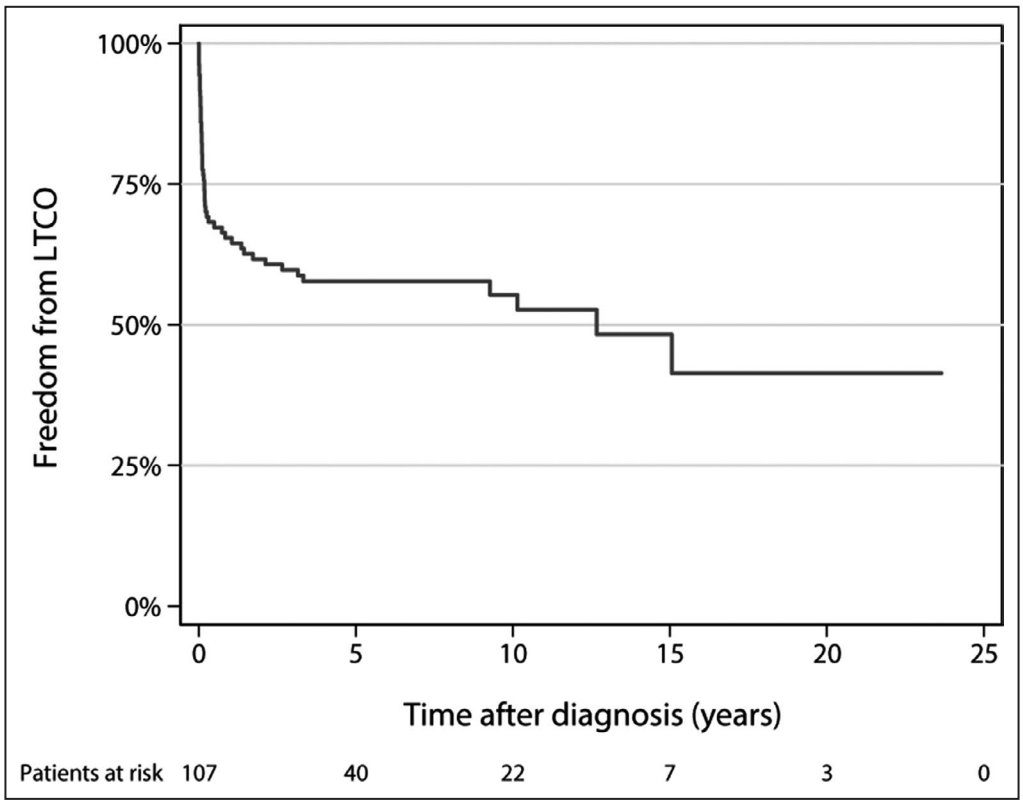

Figure 1. Kaplan–Meier analysis, time from diagnosis to life-threatening cardiac outcome (years). A life-threatening cardiac outcome (LTCO) was 1 or more of the following: resuscitated cardiac arrest, mechanical circulatory support, heart transplant, or death secondary to a cardiac cause.

An imaging diagnosis was obtained on the same day as clinical presentation in 91/96 patients (95%); the other 5 received definitive imaging within 10 days of presentation. Moderate or higher-grade mitral regurgitation was present at diagnosis in 31% of hearts (13 severe or moderate-to-severe, 15 moderate, 31 mild or mild-to-moderate, and 30 trivial or none). As expected, severity of mitral regurgitation at presentation correlated with left ventricular end-diastolic diameter (r=0.47; P<0.001).

Pathogenic Gene Variants

Forty children (37%) had at least 1 likely pathogenic/likely pathogenic (P/LP) variant in a gene associated with DCM and only a single P/LP variant was present in 37 of these 40 children. A life-threatening cardiac outcome occurred in half of patients with a P/LP variant (20/40; 19 transplants and 1 mechanical support). The 3 children with >1 P/LP variant had varying severity of clinical courses from mildly affected to arrest and transplant (Cases 12, 16, and 37 in Table S4).

In total, there were 44 P/LP variants in the cohort, and 36/44 (82%) occurred in genes encoding sarcomeric proteins (Figure 2). One or more P/LP sarcomeric variants occurred in 29 of the 40 patients with a P/LP variant (73%). *MYH7* was the gene with the greatest number of P/LP variants; 11 patients had a P/LP variant in *MYH7*.

TTN Variants in Teenage Patients

Premature termination codons, insertion/deletions, and splice-site variants in *TTN* were considered P/LP since they result in *TTN* truncations (Table S3). *TTN* truncation variants were the second most common gene mutation observed, occurring in 10 patients, with a median age of 9.7 years. Patients diagnosed with DCM as teenagers (between age 13 and 18 years) were >4 times as likely to have *TTN* truncations as those diagnosed before age 13 years (5/19 versus 5/90, P=0.01). Nonetheless, life-threatening cardiac outcomes did not exclusively occur in teenage presentations. Life-threatening cardiac outcomes occurred in 6 of the 10 patients with P/LP *TTN* variants, including 2 patients who presented before 1 year of age.

Variants of Uncertain Significance

At least 1 variants of uncertain significance (VUS) was identified in 43/109 patients (39%), of whom 30 had no P/LP variants. In contrast to the 82% of P/LP variants that were in genes encoding sarcomeric proteins, only 19% of VUS were in genes encoding sarcomeric proteins (16/85 VUS versus 36/44 P/LP, P<0.01). Neither

Table 1. Clinical Characteristics of Genotyped Pediatric DCM Cohort

	All patients (N=109)	Patients with P/LP variants (N=40)	Patients with no P/LP variants (N=69)	*P* value
Age at diagnosis, y	4.2 (5.9)	4.2 (6.1)	4.3 (5.9)	0.96
Sex				
Male	59	19	40	0.32
Female	50	21	29	
Race or ethnicity				
Black	25	7	18	0.52
Asian	7	3	4	
Hispanic	24	7	17	
White	46	21	25	
Other	7	2	5	
Life-threatening cardiac outcome*				
Yes	51	20	31	0.61
No	58	20	38	
Family history				
Yes	33	15	18	0.21
No	76	25	51	
Myocarditis history				
Yes	16	3	13	0.11
No	93	37	56	
Any arrhythmia				0.40
Yes	41	13	28	
No	68	27	41	
Ventricular arrhythmias				
Yes	27	11	16	0.62
No	82	29	53	
EF at diagnosis	29.4 (16.7)	29.3 (15.8)	29.5 (16.7)	0.95
LVEDD *Z*-score at diagnosis	4.3 (3.3)	4.0 (3.1)	4.6 (3.5)	0.44
Lowest EF	24.1 (13.2)	21.3 (12.3)	26.2 (13.6)	0.10
Largest LVEDD *Z*-score	5.1 (3.3)	5.2 (3.8)	5.0 (3.0)	0.81

Numbers in parentheses are SD in normally distributed variables. DCM indicates dilated cardiomyopathy; EF, ejection fraction; LVEDD, left ventricular end-diastolic dimension; and P/LP, pathogenic/likely pathogenic.

*"Life-threatening cardiac outcome" was 1 or more of the following: resuscitated cardiac arrest, mechanical circulatory support, heart transplantation, or death secondary to a cardiac cause.

the presence of a P/LP variant in a sarcomeric gene nor the presence of any P/LP/VUS variant in a sarcomeric gene was associated with life-threatening cardiac outcome (*P*=0.85 and 0.83, respectively).

DCM With Left Ventricular Noncompaction Features in Domain-Specific *MYH7*

All 6 children with *MYH7* variants encoding changes within amino acid residues 1 and 600 presented with a dilated cardiomyopathy with left ventricular noncompaction features (DCM-LVNC) phenotype. However, none of the 6 patients with DCM with *MYH7* variants encoding changes in amino acids 601 through 1935 had a DCM-LVNC phenotype (Figure 3).

Familial Cardiomyopathy

The subject was the proband in nearly all cases (96%); the remaining 4 patients were each the sibling of a proband. Familial cardiomyopathy was present in 33 patients (30%). Among these, 25/33 (75%) had a first-degree relative with cardiomyopathy: 14 had a parent, 14 had at least 1 sibling, and 3 had both a parent and a sibling with cardiomyopathy. Eight patients had no first-degree relatives with cardiomyopathy, but had at least 1 higher-degree relative with cardiomyopathy. The frequency of P/LP variants was not different in patients with familial cardiomyopathy (15/33 with family history versus 25/76 with no family history, *P*=0.21), but we were underpowered to detect a prevalence smaller than 26%.

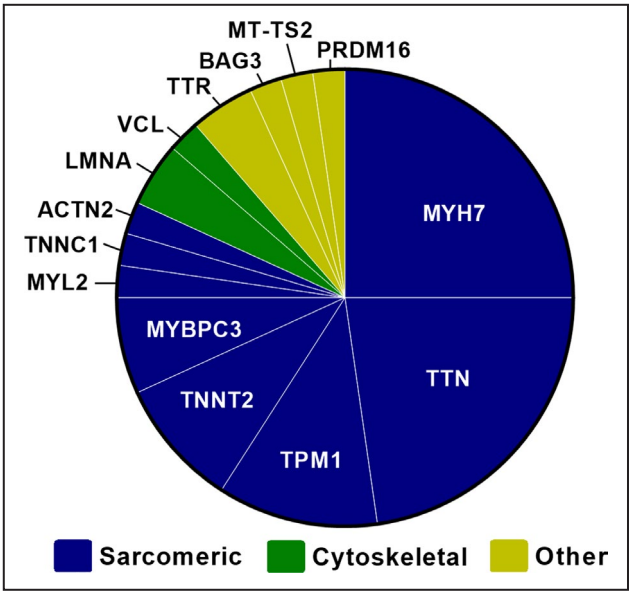

Figure 2. Distribution of genes for pathogenic and likely pathogenic variants.
Pie chart displaying the distribution of all genes containing pathogenic or likely pathogenic (P/LP) variants, weighted by the number of P/LP variants in each gene.

Additional Patient Characteristics

Of 109 genotyped DCM cases, rhythm abnormalities occurred in 41 (38%), of which 27 had ventricular arrhythmias. Among patients with ventricular arrhythmias, 11 had P/LP variants in genes associated with pediatric DCM (*MYH7*, *TNNT2*, *TPM1*, and *TTN*). The presence of a P/LP variant was not associated with a higher rate of ventricular arrhythmia (11/27 versus 31/82, P=0.82). Two patients carried P/LP variants in *TTR*, a gene that has not been associated with pediatric DCM and instead is a risk factor for late-onset adult restrictive cardiomyopathy. One patient had both *MYH7* and *TTR* P/LP variants, and 1 patient carried only a heterozygous P/LP variant in *TTR*. There is insufficient evidence to link these heterozygous *TTR* findings to a specific phenotype, but they are included here for completeness because these findings were reported in the patients' genetic testing.

Of the 16 patients (15%) who met criteria for DCM and had a clinical diagnosis of myocarditis, 10 also had positive viral testing. The viruses identified were typical myocarditis pathogens including enterovirus, coronavirus, parvovirus, and influenza. Biopsy was not routinely performed (1/16). There was no difference in the frequency of P/LP variants in patients with myocarditis (3/16) versus patients without a myocarditis diagnosis (37/93, P=0.11), nor was there any difference in life-threatening cardiac outcome (8/16 with myocarditis versus 43/93 without myocarditis, P=0.78).

Cardiac magnetic resonance imaging was performed in 35 patients, of whom 34% had P/LP variants. Delayed enhancement with gadolinium contrast was present in 10 patients, but only 1 patient had both delayed enhancement and a P/LP variant.

When considering the most stringent adjudication, where the clinical adjudication and the independent classification agreed on P/LP variants, patients with 1 or more P/LP variants were more likely to have a life-threatening cardiac outcome (15/22 with P/LP versus 36/87 without P/LP, P=0.02), perhaps suggesting that the most pathogenic variants may be associated with increased risk.

Updates in Genetic Classification

From the time when the original genetic testing was conducted, an average of 6.2 years elapsed to the time

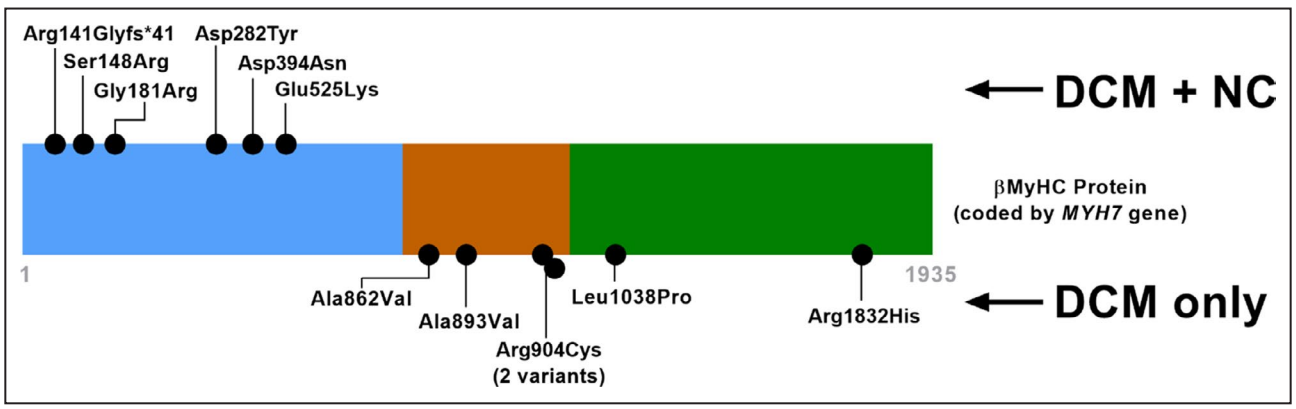

Figure 3. Domain-specific association with DCM-LVNC in *MYH7*.
Schematic illustration of each variant positioned in the 1935 amino-acid β-myosin heavy chain protein. Pediatric DCM cases with variants mapping to the head region of the protein (blue) had a phenotypic presentation of DCM and DCM-LVNC, whereas those with variants in the neck (orange) and rod (green) regions presented with DCM alone. DCM indicates dilated cardiomyopathy; DCM-LVNC, dilated cardiomyopathy with left ventricular noncompaction; and β-MyHC, β-myosin heavy chain protein.

when we re-examined and re-classified variants as part of this study (SD 2.3 years). Among 144 variants, 115 retained their original classification (6 benign/likely benign, 82 VUS, and 27 P/LP). Among the 108 variants originally adjudicated as VUS on clinical reports, 17 were updated as P/LP (16% of variants) and 9 variants were downgraded to benign/likely benign. A full disclosure of the original report classification, clinical adjudication, and the independent laboratory adjudication is provided in Table S2.

DISCUSSION

Genetic Landscape for Pediatric DCM Differs From Adult DCM

Clinical genetic testing with a gene panel identified a P/LP variant in 37% of children with DCM who were clinically genotyped in our center. An additional 28% had VUS, but no P/LP variant, and the final one third had only benign gene variants or no identified variants. Among the patients with P/LP variants, 73% had at least 1 P/LP variant in a sarcomeric gene and sarcomeric variants accounted for 82% of all P/LP variants (some patients had >1 P/LP variant). The high prevalence of sarcomeric P/LP variants contrasts with the adult data, where P/LP mutations have been described as being distributed more uniformly among genes encoding cytoskeletal, nucleoskeletal, mitochondrial, and calcium-handling proteins and there is a high prevalence of private mutations, with few hotspots or recurring mutations.[18] *LMNA*, *RBM20*, and *PLN* are common in adults, but *LMNA* P/LP variants were present in only 1.8% of cases and no P/LP variants were present in *RBM20* or *PLN* in our study population.

Overall, a *TTN* truncation variant was present in 9% of genotype-positive pediatric DCM cases. Children who presented with DCM in their teenage years were 4 times more likely to harbor a P/LP *TTN* variant than children who were identified at a younger age. This finding is consistent with prior data in nonhypertrophic cardiomyopathy and emphasizes the age-dependent risks associated with *TTN* truncating variants.[23] Others have reported *TTN* variants associated with DCM in childhood.[19,20] One important note from our study is that P/LP *TTN* variants determined by cardiac genetic testing in infancy may still be associated with life-threatening cardiac outcomes.

However, these associations do not prove causality in pediatric DCM. For example, 1 patient had 2 *TTN* variants in *cis*, each predicted to result in protein truncation (Case 37). We cannot determine from these data whether 1, both, or neither variant caused *TTN*-related clinical disease. Similarly, gene testing panels identified 2 cases with pathogenic *TTR* variants, which are typically associated with late-onset familial amyloid cardiomyopathy (Cases 16 and 39). One *TTR* variant was observed in a patient who also had a pathogenic *MYH7* variant. The other was seen in a toddler who presented with heart failure and ventricular arrhythmias but did not otherwise have typical features of familial amyloid cardiomyopathy. The late-onset nature of *TTR* cardiomyopathy is well established, but to be comprehensive, all variants classified as pathogenic were included in the results.

Domain-Specific *MYH7* Gene Variants Are Associated With DCM-LVNC

MYH7 has been reported in only 3% to 4% in adult-onset DCM, whereas a P/LP variant in *MYH7* occurred in 10% of patients in this pediatric cohort.[2,12] As an important additional finding, our data support a domain-specific variation *MYH7* associated with DCM-LVNC. In adult DCM, *MYH7* mutations associated with noncompaction have been described clustering into amino acids near the ATP binding site.[21] Recent studies have correlated DCM-LVNC with *MYH7* mutations beyond the ATPase site.[22,23] We found that all patients with *MYH7* variants and DCM-LVNC had variants of interest encoding the first 600 amino acids of β-myosin heavy chain (the head region), whereas none of the patients with variants encoding the later amino acids had DCM-LVNC.

Clinical Genetic Testing

All variants were obtained from panels ordered during clinical care. The yield of P/LP variants in this cohort supports the use of panels in children with DCM, and these data have allowed us to effectively perform cascade screening in families. In a secondary analysis, a family history of cardiomyopathy did not affect the frequency of P/LP variants. Until larger data sets are available, we continue to recommend that all children with idiopathic DCM receive genetic testing, not just those with a positive family history.

In addition, 13% of VUS were adjudicated as P/LP variants when reclassified an average of 6 years later. Families need to be educated that reclassification may change the implications for clinical care and family screening. This is consistent with data previously published in pediatric cardiology, demonstrating the long-term value in a centralized program with access to genetic counseling and variant re-adjudication.[24] Finally, the 2015 American College of Medical Genetics guidelines improved variant adjudication, but did not make it entirely uniform. We found differences between our clinical adjudication and the classifications made by an independent laboratory. However, the variations in classification were because of reasonable differences in application of individual American College of Medical Genetics criteria, as has been documented elsewhere.[25]

Limitations

This was a single-center retrospective review and may have selection bias toward those with worse outcomes or presentation because of the referral nature of our pediatric heart transplant center. Selection bias may impact our finding of a high prevalence of sarcomeric variants. The genes tested by the various commercial gene panels changed over time and may have biased our retrospective findings (reported in Table S1). However, these data represent a typical use of clinical genetic panels over the last 15 years. As cost and barriers to access for genetic testing continue to fall and postsequencing bioinformatics improves, a broader genotype–phenotype analysis may be possible in the future. In addition, we recognize the differences in approaches to variant classification and provide Table S4 as a full comparison of the 3 classification systems used in this article.

CONCLUSIONS

This pediatric DCM cohort had a high frequency of sarcomeric gene variants. *TTN* truncations were more common in teenagers who presented with DCM, but infants were not spared, despite TTN's genetic profile as a late-onset form of DCM in adults. VUS were important in this patient population, because our data suggest that many of them may be reclassified as pathogenic or likely pathogenic in the future. Finally, we provided pediatric data to support a domain-specific link between *MYH7* and a DCM-LVNC phenotype. In summary, these data suggest genotype–phenotype correlations that emphasize the importance of clinical genetic testing in pediatric DCM.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Tables S1–S4

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SUPPLEMENTAL MATERIAL

Table S1: Gene Panels
Khan et al. Genotype and Cardiac Outcomes in Pediatric Dilated Cardiomyopathy, 2021

Gene	Harvard Partners LMM 2007	Harvard Partners LMM 2009	GeneDx 2009	Transgenomic/ Familion 2009	Harvard Partners LMM 2011	GeneDx DCM 2011	Transgenomic/ Familion 2011	Harvard Partners LMM 2013	GeneDx 2013	Transgenomic/ Familion 2013	GeneDx 2017*	Invitae 2017*
ABCC9		✓			✓			✓			✓	✓
ACTC	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ACTN2		✓			✓			✓	✓		✓	✓
AGL												✓
ALMS1											✓	
APLK3											✓	
ANKRD1					✓		✓	✓	✓	✓	✓	✓
BAG3								✓			✓	✓
BRAF											✓	
CACNA1C												✓
CALR3												✓
CASQ2					✓			✓				
CAV3					✓			✓			✓	✓
CHRM2											✓	✓
CRYAB					✓			✓			✓	✓
CSRP3		✓			✓			✓	✓		✓	✓
CTF1		✓			✓			✓				✓
CTNNA3												✓
DES		✓	✓		✓	✓		✓	✓		✓	✓
DMD											✓	✓
DOLK											✓	✓

Gene	Harvard Partners LMM 2007	Harvard Partners LMM 2009	GeneDx 2009	Transgenomic/ Familion 2009	Harvard Partners LMM 2011	GeneDx DCM 2011	Transgenomic/ Familion 2011	Harvard Partners LMM 2013	GeneDx 2013	Transgenomic/ Familion 2013	GeneDx 2017*	Invitae 2017*
DSC2					✓			✓			✓	✓
DSG2					✓			✓			✓	✓
DSP					✓			✓			✓	✓
DTNA					✓			✓			✓	✓
EMD		✓			✓			✓	✓		✓	✓
EYA4												✓
FHL1											✓	✓
FHL2					✓			✓				✓
FKRP											✓	✓
FKTN											✓	✓
FLNC												✓
GAA												✓
GATA4												✓
GATA6												✓
GATAD1								✓			✓	✓
GLA				✓	✓			✓			✓	✓
HCN4											✓	✓
HRAS											✓	
ILK											✓	✓
JPH2											✓	✓
JUP					✓			✓			✓	✓
KRAS											✓	
LAMA4					✓			✓			✓	✓
LAMP2			✓	✓	✓	✓		✓	✓		✓	✓

Gene	Harvard Partners LMM 2007	Harvard Partners LMM 2009	GeneDx 2009	Transgenomic/ Familion 2009	Harvard Partners LMM 2011	GeneDx DCM 2011	Transgenomic/ Familion 2011	Harvard Partners LMM 2013	GeneDx 2013	Transgenomic/ Familion 2013	GeneDx 2017*	Invitae 2017*
LDB3/ZASP	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
LMNA	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
LRRC10												✓
MAP2K1											✓	
MAP2K2											✓	
MIB1											✓	
MTND1 (NADH dehydro1)			✓			✓			✓		✓	
MTND5 (NADH dehydro5)			✓			✓			✓		✓	
MTND6 (NADH dehydro6)			✓			✓			✓		✓	
MTTD (tRNA Asp)						✓			✓		✓	
MTTG (tRNA Gly)											✓	
MTTH (tRNA His)			✓			✓			✓		✓	
MTTI (tRNA Ile)						✓			✓		✓	
MTTK (tRNA Lys)			✓			✓			✓		✓	
MTTL1 (tRNA Leu)			✓			✓			✓		✓	
MTTL2 (tRNA Leu2)						✓			✓		✓	
MTTM (methionine)						✓			✓		✓	
MTTQ (tRNA Gln)			✓			✓			✓		✓	
MTTS1 (tRNA Ser1)			✓			✓			✓		✓	
MTTS2 (tRNA Ser2)			✓			✓			✓		✓	
MURC											✓	
MYBPC3	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Gene	Harvard Partners LMM 2007	Harvard Partners LMM 2009	GeneDx 2009	Transgenomic/ Familion 2009	Harvard Partners LMM 2011	GeneDx DCM 2011	Transgenomic/ Familion 2011	Harvard Partners LMM 2013	GeneDx 2013	Transgenomic/ Familion 2013	GeneDx 2017*	Invitae 2017*
MYH6					✓			✓			✓	✓
MYH7	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MYL2				✓	✓						✓	✓
MYL3				✓	✓			✓			✓	✓
MYLK2					✓			✓			✓	✓
MYOM1												✓
MYOZ2					✓			✓			✓	✓
MYPN											✓	✓
NEBL								✓			✓	✓
NEXN					✓			✓	✓		✓	✓
NKX2.5											✓	✓
NPPA												✓
NRAS											✓	
PDLIM3											✓	✓
PKP2					✓			✓			✓	✓
PLEKHM2												✓
PLN	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
PRDM16											✓	✓
PRKAG2				✓	✓			✓			✓	✓
PTPN11											✓	
RAF1											✓	✓
RBM20					✓			✓	✓		✓	✓
RIT1											✓	
RYR2					✓			✓			✓	✓

Gene	Harvard Partners LMM 2007	Harvard Partners LMM 2009	GeneDx 2009	Transgenomic/ Familion 2009	Harvard Partners LMM 2011	GeneDx DCM 2011	Transgenomic/ Familion 2011	Harvard Partners LMM 2013	GeneDx 2013	Transgenomic/ Familion 2013	GeneDx 2017*	Invitae 2017*
SCN5A							✓	✓	✓	✓	✓	✓
SGCD		✓	✓		✓			✓	✓		✓	✓
SLC22A5												✓
SOS1											✓	
TAZ	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
TCAP		✓			✓			✓			✓	✓
TGFB3					✓				✓		✓	✓
TMEM43								✓				✓
TMPO								✓			✓	✓
TNNC1				✓	✓		✓	✓	✓	✓	✓	✓
TNNI3	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TNNT2	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TPM1	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TTN					✓			✓	✓		✓	✓
TTR			✓		✓	✓		✓	✓		✓	✓
TXNRD2											✓	✓
VCL		✓			✓			✓	✓		✓	✓

LMM = Laboratory for Molecular Medicine; * = deletion/duplication added in 2016

Table S2: Genotype and Variant Classification
Khan et al. Genotype and Cardiac Outcomes in Pediatric Dilated Cardiomyopathy, 2021

Gene	DNA change	Protein effect	Clinical Adjudication	Original Report Classification	External Lab Classification	Case Number [a]
ACTN2	c.26A>G	p.Gln9Arg	VUS	P	VUS	104
ACTN2	c.26A>G	p.Gln9Arg	VUS	LP	VUS	106
ACTN2	c.2630dupG	p.Ala878Cysfs*62	P/LP	VUS	VUS	1
BAG3	c.367C>T	p.Arg123X	P/LP	P	P/LP	2
LMNA	c.350A>G	p.Lys117Arg	P/LP	VUS	VUS	4
LMNA	c.868G>A	p.Glu290Lys	P/LP	VUS	P/LP	3
MT-TS2	m.12241delC		P/LP	LP	Not provided	5
MYBPC3	c.1721G>A	p.Arg574Gln	P/LP	VUS	VUS	7
MYBPC3	c.1294G>A	p.Ala432Thr	P/LP	VUS	VUS	8
MYBPC3	c.3628-41_3628-17del25	IVS32-41_IVS32-17del25	P/LP	VUS	P/LP	6
MYH7	c.3113T>C	p.Leu1038Pro	P/LP	LP	VUS	12
MYH7	c.2678C>T	p.Ala893Val	P/LP	VUS	P/LP	9
MYH7	c.4280A>T	p.Asp1427Val	P/LP	LP	VUS	17
MYH7	c.444C>G	p.Ser148Arg	P/LP	VUS	VUS	18
MYH7	c.1180G>A	p.Asp394Asn	P/LP	VUS	VUS	10
MYH7	c.541G>A	p.Gly181Arg	P/LP	VUS	VUS	15
MYH7	c.2585C>T	p.Ala862Val	P/LP	LP	VUS	16
MYH7	c.2711G>A	p.Arg904His	P/LP	P	P/LP	11
MYH7	c.844G>T	p.Asp282Tyr	P/LP	VUS	VUS	14
MYH7	c.1573G>A	p.Glu525Lys	P/LP	VUS	P/LP	13
MYH7	c.2710C>T	p.Arg904Cys	P/LP	P	P/LP	19
MYL2	c.401A>C	p.Glu134Ala	P/LP	P	VUS	12
PRDM16	c.1573dupC	p.Arg525Profs*79	P/LP	P	P/LP	20
TNNC1	c.184G>A	p.Asp62Asn	P/LP	VUS	VUS	21
TNNT2	c.421C>T	p.Arg141Trp	P/LP	P	P/LP	22
TNNT2	c.391C>T	p.Arg131Trp	P/LP	LP	P/LP	24
TNNT2	c.392G>A	p.Arg131Gln	P/LP	LP	P/LP	23
TNNT2	c.352G>A	p.Glu118Lys	P/LP	LP	VUS	25
TPM1	c.725C>T	p.Ala242Val	P/LP	P	VUS	27
TPM1	c.479G>A	p.Arg160His	P/LP	LP	P/LP	28
TPM1	c.118G>C	p.Glu40Gln	P/LP	VUS	VUS	29
TPM1	c.725C>T	p.Ala242Val	P/LP	P	VUS	26
TPM1	c.688G>A	p.Asp230Asn	P/LP	P	P/LP	30
TTN	c.28363+1G>A	Splice variant	P/LP	VUS	VUS	32
TTN	c.75793C>T	p.Arg25265*	P/LP	P	P/LP	34
TTN	c.92206_92207dupTA	p.Leu30738Hisfs*4	P/LP	P	P/LP	35
TTN	c.75703delG	p.Val25235Serfs*68	P/LP	LP	P/LP	38
TTN	c.94261_94262 dupGG	p.Leu31422Valfs*20	P/LP	P	P/LP	33
TTN	c.1800+1G>A	Splice variant	P/LP	LP	VUS	37
TTN	c.62572C>T	p.Arg20858*	P/LP	P	P/LP	36
TTN	c.102712C>T	p.Gln34238*	P/LP	VUS	P/LP	12
TTN	c.16387_16390delATCT	p.Ile5463Valfs*15	P/LP	VUS	VUS	37
TTN	c.73828G>T	p.Glu24610*	P/LP	LP	P/LP	31
TTR	c.424G>A	p.Val142Ile	P/LP	P	P/LP	16
TTR	c.424G>A	p.Val142Ile	P/LP	P	P/LP	39
VCL	c.562C>T	p.Arg188*	P/LP	P	VUS	40
			VUS only below			
ACTC1	c.623G>A	p.Arg208His	VUS	VUS	VUS	86
ACTC1	c.579G>T	p.Lys193Asn	VUS	VUS	VUS	61
ACTC1	c.119_129+14del25	p.Pro40Argfs*15	VUS	VUS	VUS	86
ACTN2	c.2306A>C	p.Lys769Thr	VUS	VUS	VUS	96
ACTN2	c.578_583del	p.His193_Arg194del	VUS	VUS	VUS	96
ACTN2	c.548G>A	p.Gly183Asp	VUS	VUS	VUS	47
ACTN2	c.1984C>T	p.Arg662Trp	VUS	VUS	VUS	11
ALMS1	c.11711G>A	p.Arg3904Gln	VUS	VUS	VUS	29
BAG3	c.474_476dup	p.Ala160dup	VUS	VUS	B/LB	96
CTF1	c.275C>A	p.Ala92Glu	VUS	VUS	VUS	24
DES	c.1009G>A	p.Ala337Thr	VUS	VUS	VUS	82
DES	c.935A>C	p.Asp312Ala	VUS	VUS	VUS	78
DES	c.170C>T	p.Ser57Leu	VUS	VUS	VUS	47
DES	c.934G>A	p.Asp312Asn	VUS	VUS	VUS	79
DMD	c.404A>G	p.Asn135Ser	VUS	VUS	VUS	77
DMD	c.9299A>G	p.Asn3100Ser	VUS	VUS	VUS	106
DSC2	c.1914G>C	p.Gln638His	VUS	VUS	B/LB	39
DSC2	c.1081G>A	p.Val361Met	VUS	VUS	VUS	61
DSC2	c.2446G>A	p.Val816Met	VUS	VUS	VUS	34
DSC2	c.26C>G	p.Ser9Cys	VUS	VUS	VUS	74

Table S2: Genotype and Variant Classification
Khan et al. Genotype and Cardiac Outcomes in Pediatric Dilated Cardiomyopathy, 2021

Gene	DNA change	Protein effect	Clinical Adjudication	Original Report Classification	External Lab Classification	Case Number [a]
DSP	c.2287T>C	p.Tyr763His	VUS	VUS	VUS	20
DSP	c.607G>A	p.Asp203Asn	VUS	VUS	VUS	100
DSP	c.4288A>T	p.Ile1430Phe	VUS	VUS	VUS	71
DSP	c.88G>A	p.Val30Met	B/LB	VUS	VUS	68
DSP	c.269A>G	p.Gln90Arg	VUS	VUS	VUS	11
DSP	c.4172A>G	p.Tyr1391Cys	VUS	VUS	VUS	50
DSP	c.2723G>A	p.Arg908His	VUS	VUS	VUS	35
DSP	c.1778A>G	p.Asn593Ser	VUS	VUS	B/LB	31
DSP	c.107G>C	p.Gly36Ala	VUS	VUS	VUS	34
DSP	c.8529_8540del12	p.Ser2843_Arg2846del	VUS	VUS	VUS	78
DSP	c.4372C>G	p.Arg1458Gly	VUS	VUS	VUS	29
DTNA	c.1228G>A	p.Asp410Asn	VUS	VUS	VUS	98
FKRP	c.404C>A	p.Ala135Asp	VUS	VUS	VUS	52
FLNC	c.6539G>A	p.Arg2180His	VUS	VUS	VUS	108
GLA	c.1153A>G	p.Thr385Ala	VUS	VUS	B/LB	61
GLA	c.427G>A	p.Ala143Thr	VUS	VUS	VUS	39
ILK	c.184G>A	p.Val62Ile	VUS	VUS	VUS	90
LAMA4	c.2599C>G	p.Leu867Val	VUS	VUS	VUS	29
LAMA4	c.2069G>A	p.Arg690His	VUS	VUS	VUS	51
LAMA4	c.1612C>T	p.Arg538Cys	VUS	VUS	B/LB	105
LDB3	c.752A>G	p.Lys251Arg	B/LB	LB	B/LB	15
LDB3	c.1606G>T	p.Val536Phe	VUS	VUS	VUS	39
LDB3	c.566C>T	p.Ser189Leu	VUS	VUS	VUS	52
LMNA	c.861T>C	Ala287Ala	B/LB	B	B/LB	13
MYBPC3	c.2980C>T	p.Leu994Phe	VUS	VUS	VUS	106
MYBPC3	c.472G>A	p.Val158Met	B/LB	LB	B/LB	72
MYBPC3	c.2870C>G	p.Thr957Ser	VUS	VUS	B/LB	12
MYBPC3	c.3682C>T	p.Arg1228Cys	VUS	VUS	VUS	100
MYBPC3	c.1519G>A	p.Gly507Arg	B/LB	VUS	B/LB	80
MYBPC3	c.472G>A	p.Val158Met	B/LB	LB	B/LB	21
MYH6	c.2401A>G	p.Ile801Val	VUS	VUS	VUS	98
MYH6	c.5089A>G	p.Thr1697Ala	VUS	VUS	VUS	73
MYH6	c.4293G>A	p.Met1431Ile	VUS	VUS	VUS	9
MYH6	c.3979-7_3979-6delTC		VUS	VUS	VUS	73
MYH7	c.5495G>A	p.Arg1832His	VUS	VUS	VUS	36
MYL2	c.141C>A	p.Asn47Lys	VUS	VUS	VUS	74
MYLK2	c.4G>A	p.Ala2Thr	B/LB	VUS	VUS	92
MYPN	c.1130G>A	p.Arg377Gln	B/LB	VUS	VUS	109
MYPN	c.3481C>A	p.Leu1161Ile	VUS	VUS	B/LB	47
MYPN	c.-166-1G>C	Splice variant	VUS	VUS	VUS	89
MYPN	c.1594G>A	p.Val532Met	VUS	VUS	VUS	35
NEBL	c.604G>A	p.Gly202Arg	VUS	VUS	VUS	2
NEBL	c.180G>C	p.Lys60Asn	B/LB	VUS	VUS	87
NKX2-5	c.632C>T	p.Pro211Leu	VUS	VUS	VUS	81
PDLIM3	c.926G>A	p.Arg309Gln	VUS	VUS	VUS	35
PDLIM3	c.697G>C	p.Val233Leu	B/LB	VUS	VUS	88
PRDM16	c.2815C>G	p.Leu939Val	VUS	VUS	VUS	11
PRKAG2	c.64G>T	p.Gly22Cys	VUS	VUS	VUS	64
RAF1	c.1721A>G	p.Tyr574Cys	VUS	VUS	VUS	95
RAF1	c.293T>C	p.Val98Ala	VUS	VUS	VUS	36
RBM20	c.1459G>A	p.Val487Met	VUS	LB	VUS	42
RBM20	c.3301G>A	p.Glu1101Lys	VUS	VUS	VUS	64
RBM20	c.2662G>A	p.Asp888Asn	VUS	VUS	B/LB	100
RBM20	c.2565_2570delACAGGA	p.Gln856_Glu857del	VUS	VUS	VUS	71
RBM20	c.2662G>A	p.Asp888Asn	VUS	VUS	B/LB	76
RYR2	c.6337G>A	p.Val2113Met	VUS	VUS	VUS	53
RYR2	c.2984T>C	p.Met995Thr	VUS	VUS	VUS	47
SCN5A	c.1425A>C	p.Arg475Ser	VUS	VUS	VUS	34
SCN5A	c.1820G>A	p.Gly607Asp	VUS	VUS	VUS	54
SCN5A	c.5972G>A	p.Arg1991Gln	VUS	VUS	VUS	50
SCN5A	c.2314G>A	p.Asp772Asn	VUS	VUS	VUS	76
SCN5A	c.1673A>G	p.His558Arg	B/LB	LB	B/LB	93
SCN5A	c.4342A>C	p.Ile1448Leu	VUS	VUS	VUS	53
SCN5A	c.3308C>A	p.Ser1103Tyr	B/LB	VUS	VUS	91
SGCD	c.717C>G	p.Asp239Glu	VUS	VUS	B/LB	71
SGCD	c.15G>C	p.Glu5Asp	B/LB	VUS	B/LB	41
SGCD	c.458A>G	p.Asp153Gly	VUS	VUS	VUS	47

Table S2: Genotype and Variant Classification
Khan et al. Genotype and Cardiac Outcomes in Pediatric Dilated Cardiomyopathy, 2021

Gene	DNA change	Protein effect	Clinical Adjudication	Original Report Classification	External Lab Classification	Case Number [a]
SOS2	c.3443_3454del	p.Pro1148_Pro1151del	VUS	VUS	VUS	108
TAZ	c.383T>C	p.Phe128Ser	B/LB	VUS	B/LB	99
TAZ	c.383T>C	p.Phe128Ser	B/LB	LB	B/LB	15
TMEM43	c.286C>G	p.Arg96Gly	VUS	VUS	VUS	78
TMPO	c.694C>T	p.Pro232Ser	VUS	VUS	VUS	36
TNNT2	c.224T>G	p.Val75Gly	VUS	VUS	VUS	93
TNNT2	c.178A>G	p.Met60Val	VUS	VUS	B/LB	22
TNNT2	c.178A>C	p.Met60Leu	VUS	VUS	VUS	53
TNNT2	c.587G>A	p.Arg196Gln	VUS	VUS	VUS	36
TTN	c.40166_40168delAAG	p.Glu13389del	VUS	VUS	VUS	106
VCL	c.2285G>A	p.Arg762Gln	VUS	VUS	VUS	12

[a] Case number is the same as in Table S4.

Table S3: Additional *TTN* Information
Khan et al. Genotype and Cardiac Outcomes in Pediatric Dilated Cardiomyopathy Patients, 2021

Gene	DNA change	Protein effect	Transcript Sequenced	Exon	PSI[a]	Protein Location	Case Number[b]
TTN	c.73828G>T	p.Glu24610*	NM_133378.4	275	100	A-band	31
TTN	c.28363+1G>A	Splice variant	NM_133378.4	122	54	I-band	32
TTN	c.102712C>T	p.Gln34238*	NM_001256850.1	312	100	A-band	12
TTN	c.94261_94262 dupGG	p.Leu31422Valfs*20	NM_001256850.1	304	100	A-band	33
TTN	c.75793C>T	p.Arg25265*	NM_001256850.1	276	100	A-band	34
TTN	c.92206_92207dupTA	p.Leu30738Hisfs*4	NM_001256850.1	298	100	A-band	35
TTN	c.62572C>T	p.Arg20858*	NM_001256850.1	269	100	A-band	36
TTN	c.1800+1G>A	Splice variant	NM_133378.4	I11[c]	N/A	Z-disk	37
TTN	c.16387_16390delATCT	p.Ile5463Valfs*15	NM_133379.3	45A	N/A	N/A	37
TTN	c.75703delG	p.Val25235Serfs*68	NM_133378.4	275	100	A-band	38
TTN	c.40166_40168delAAG	p.Glu13389del	NM_001256850.1	195	5	N/A	106

[a] PSI: Percentage spliced-in. The data shown represent exon usage in the human left ventricle, derived from patients with DCM and were obtained from Royal Brompton & Harefield (NHS Foundation Trust) at https://www.cardiodb.org/titin/titin_transcripts.php, accessed 15 Jun 2021.

[b] Case number is the same as in Table S4.

[c] Intron 11. Located in the invariant region (± 1,2) of the splice consensus sequence and predicted to cause altered splicing

Table S4: Phenotype and Genotype
Khan et al. Genotype and Cardiac Outcomes in Pediatric Dilated Cardiomyopathy, 2021

Case Number	Female Sex	Age at Presentation (Years)	Family History	Life-Threatening Cardiac Outcome	Ventricular Arrhythmia	Cardiac Arrest	Mechanical Support	Transplant	Death	Gene	cDNA	Protein	Year of Genetic Test
1	1	0	No family history	0	0	0	0	0	0	ACTN2	c.2630dupG	p.Ala878Cysfs*62	2016
2	1	0	No family history	1	0	0	1	1	0	BAG3	c.367C>T	p.Arg123*	2015
3	1	6	No family history	1	0	0	1	1	0	LMNA	c.868G>A	p.Glu290Lys	2017
4	1	1	No family history	0	0	0	0	0	0	LMNA	c.350A>G	p.Lys117Arg	2010
5	0	2	No family history	0	0	0	0	0	0	MT-TS2	m.12241delC		2015
6	0	0	1st degree FH	1	0	0	0	1	0	MYBPC3	c.3628-41_3628-17del25	IVS32-41_IVS32-17del25	2016
7	0	14	No family history	1	0	0	0	1	0	MYBPC3	c.1721G>A	p.Arg574Gln	2009
8	1	0	No family history	0	0	0	0	0	0	MYBPC3	c.1294G>A	p.Ala432Thr	2013
9	0	0	No family history	1	0	0	0	1	0	MYH7	c.2678C>T	p.Ala893Val	2014
10	1	0	No family history	1	0	0	1	1	0	MYH7	c.1180G>A	p.Asp394Asn	2012
11	0	0	1st degree FH	1	1	0	1	1	0	MYH7	c.2711G>A	p.Arg904His	2016
12	0	0	1st degree FH	1	0	1	0	1	0	MYH7	c.3113T>C	p.Leu1038Pro	2015
12	0	0	1st degree FH	1	0	1	0	1	0	MYL2	c.401A>C	p.Glu134Ala	2015
12	0	0	1st degree FH	1	0	1	0	1	0	TTN	c.102712C>T	p.Gln34238*	2015
13	1	0	No family history	1	0	0	1	1	0	MYH7	c.1573G>A	p.Glu525Lys	2008
14	1	0	1st degree FH	0	0	0	0	0	0	MYH7	c.844G>T	p.Asp282Tyr	2012
15	0	5	1st degree FH	0	0	0	0	0	0	MYH7	c.541G>A	p.Gly181Arg	2012
16	0	18	No family history	0	1	0	0	0	0	MYH7	c.2585C>T	p.Ala862Val	2015
16	0	18	No family history	0	1	0	0	0	0	TTR	c.424G>A	p.Val142Ile	2015
17	1	3	1st degree FH	0	0	0	0	0	0	MYH7	c.4280A>T	p.Asp1427Val	2014
18	1	0	No family history	0	0	0	0	0	0	MYH7	c.444C>G	p.Ser148Arg	2017
19	1	10	No family history	1	1	0	0	1	0	MYH7	c.2710C>T	p.Arg904Cys	2009
20	0	0	No family history	0	0	0	0	0	0	PRDM16	c.1573dupC	p.Arg525Profs*79	2016
21	1	15	1st degree FH	0	0	0	0	0	0	TNNC1	c.184G>A	p.Asp62Asn	2013
22	1	0	No family history	1	0	0	1	1	1	TNNT2	c.421C>T	p.Arg141Trp	2011
23	0	0	No family history	0	1	0	0	0	0	TNNT2	c.392G>A	p.Arg131Gln	2009
24	1	5	1st degree FH	0	0	0	0	0	0	TNNT2	c.391C>T	p.Arg131Trp	2013
25	0	0	No family history	1	1	0	0	1	0	TNNT2	c.352G>A	p.Glu118Lys	2013
26	1	0	1st degree FH	0	0	0	0	0	0	TPM1	c.725C>T	p.Ala242Val	2009
27	0	0	1st degree FH	0	0	0	0	0	0	TPM1	c.725C>T	p.Ala242Val	2009
28	1	0	No family history	1	0	0	0	1	0	TPM1	c.479G>A	p.Arg160His	2010
29	0	0	No family history	1	1	0	0	1	0	TPM1	c.118G>C	p.Glu40Gln	2017
30	1	0	1st degree FH	0	0	0	0	0	0	TPM1	c.688G>A	p.Asp230Asn	2007
31	1	6	1st degree FH	1	0	0	1	1	0	TTN	c.73828G>T	p.Glu24610*	2012
32	0	0	No family history	0	0	0	0	0	0	TTN	c.28363+1G>A		2013
33	0	18	1st degree FH	0	0	0	0	0	0	TTN	c.94261_94262 dupGG	p.Leu31422Valfs*20	2014
34	0	15	1st degree FH	0	1	0	0	0	0	TTN	c.75793C>T	p.Arg25265*	2016
35	0	16	No family history	1	1	0	1	1	0	TTN	c.92206_92207dupTA	p.Leu30738Hisfs*4	2014
36	1	13	No family history	1	1	0	0	1	0	TTN	c.62572C>T	p.Arg20858*	2016
37	0	1	Higher degree FH	0	0	0	0	0	0	TTN	c.1800+1G>A	Splice variant	2012
37	0	1	Higher degree FH	0	0	0	0	0	0	TTN	c.16387_16390delATCT	p.Ile5463Valfs*15	2012
38	0	14	No family history	1	1	0	0	1	0	TTN	c.75703delG	p.Val25235Serfs*68	2013
39	1	2	No family history	1	1	0	1	0	0	TTR	c.424G>A	p.Val142Ile	2015
40	1	0	No family history	1	0	0	0	1	0	VCL	c.562C>T	p.Arg188*	2010

Table S4: Phenotype and Genotype
Khan et al. Genotype and Cardiac Outcomes in Pediatric Dilated Cardiomyopathy, 2021

Case Number	Female Sex	Age at Presentation (Years)	Family History	Life-Threatening Cardiac Outcome	Ventricular Arrhythmia	Cardiac Arrest	Mechanical Support	Transplant	Death	Gene	cDNA	Protein	Year of Genetic Test
41	0	1	No family history	0	0	0	0	0	0	No P/LP Variants			
42	1	0	Higher degree FH	0	0	0	0	0	0	No P/LP Variants			
43	0	0	Higher degree FH	0	0	0	0	0	0	No P/LP Variants			
44	1	12	No family history	0	1	0	0	0	0	No P/LP Variants			
45	0	13	No family history	1	0	0	0	1	0	No P/LP Variants			
46	0	3	No family history	1	0	0	1	0	1	No P/LP Variants			
47	0	0	No family history	0	0	0	0	0	0	No P/LP Variants			
48	1	0	No family history	0	0	0	0	0	0	No P/LP Variants			
49	0	15	No family history	0	0	0	0	0	0	No P/LP Variants			
50	0	0	No family history	1	0	0	0	1	0	No P/LP Variants			
51	0	0	No family history	0	0	0	0	0	0	No P/LP Variants			
52	1	0	Higher degree FH	0	0	0	0	0	0	No P/LP Variants			
53	1	8	No family history	1	1	1	1	1	0	No P/LP Variants			
54	0	0	No family history	0	0	0	0	0	0	No P/LP Variants			
55	0	10	1st degree FH	1	1	1	0	1	0	No P/LP Variants			
56	0	0	1st degree FH	1	0	0	0	1	1	No P/LP Variants			
57	0	2	No family history	0	0	0	0	0	0	No P/LP Variants			
58	0	12	No family history	0	0	0	0	0	0	No P/LP Variants			
59	1	0	No family history	1	1	0	0	1	1	No P/LP Variants			
60	0	1	Higher degree FH	1	0	0	1	1	0	No P/LP Variants			
61	0	0	1st degree FH	0	0	0	0	0	0	No P/LP Variants			
62	1	0	1st degree FH	1	0	0	0	1	0	No P/LP Variants			
63	1	13	1st degree FH	1	0	0	0	1	0	No P/LP Variants			
64	1	1	No family history	0	0	0	0	0	0	No P/LP Variants			
65	1	1	No family history	0	0	0	0	0	0	No P/LP Variants			
66	0	14	No family history	0	1	0	0	0	0	No P/LP Variants			
67	0	0	No family history	1	0	0	0	1	0	No P/LP Variants			
68	1	13	No family history	0	1	0	0	0	0	No P/LP Variants			
69	0	10	No family history	1	0	0	0	1	1	No P/LP Variants			
70	0	16	No family history	0	1	0	0	0	0	No P/LP Variants			
71	1	0	No family history	0	0	0	0	0	0	No P/LP Variants			
72	0	1	1st degree FH	0	0	0	0	0	0	No P/LP Variants			
73	0	1	No family history	0	0	0	0	0	0	No P/LP Variants			
74	1	0	No family history	0	0	0	0	0	0	No P/LP Variants			
75	0	0	No family history	1	0	0	0	1	0	No P/LP Variants			
76	0	10	1st degree FH	1	0	0	0	1	0	No P/LP Variants			
77	1	0	No family history	1	0	1	0	1	0	No P/LP Variants			
78	1	1	No family history	1	1	1	0	0	0	No P/LP Variants			
79	0	17	Higher degree FH	0	1	0	0	0	0	No P/LP Variants			
80	1	0	No family history	1	0	0	0	1	0	No P/LP Variants			
81	0	0	No family history	0	0	0	0	0	0	No P/LP Variants			
82	1	0	No family history	0	0	0	0	0	0	No P/LP Variants			
83	0	1	Higher degree FH	1	0	0	0	1	0	No P/LP Variants			
84	0	4	Higher degree FH	1	0	0	0	1	0	No P/LP Variants			

Table S4: Phenotype and Genotype
Khan et al. Genotype and Cardiac Outcomes in Pediatric Dilated Cardiomyopathy, 2021

Case Number	Female Sex	Age at Presentation (Years)	Family History	Life-Threatening Cardiac Outcome	Ventricular Arrhythmia	Cardiac Arrest	Mechanical Support	Transplant	Death	Gene	cDNA	Protein	Year of Genetic Test
85	0	1	No family history	0	0	0	0	0	0	No P/LP Variants			
86	1	0	1st degree FH	0	0	0	0	0	0	No P/LP Variants			
87	1	0	No family history	0	0	0	0	0	0	No P/LP Variants			
88	0	0	No family history	0	0	0	0	0	0	No P/LP Variants			
89	1	4	No family history	1	1	1	1	0	0	No P/LP Variants			
90	0	1	No family history	0	0	0	0	0	0	No P/LP Variants			
91	0	1	No family history	0	0	0	0	0	0	No P/LP Variants			
92	0	16	1st degree FH	1	0	0	0	0	1	No P/LP Variants			
93	1	0	No family history	0	0	0	0	0	0	No P/LP Variants			
94	1	7	No family history	1	1	0	0	1	0	No P/LP Variants			
95	0	0	No family history	1	0	0	0	1	0	No P/LP Variants			
96	0	1	No family history	1	0	0	0	1	1	No P/LP Variants			
97	1	0	No family history	1	1	1	1	1	0	No P/LP Variants			
98	0	15	1st degree FH	0	0	0	0	0	0	No P/LP Variants			
99	1	2	No family history	0	1	0	0	0	0	No P/LP Variants			
100	0	0	No family history	1	0	0	0	1	0	No P/LP Variants			
101	1	1	No family history	1	1	0	1	1	0	No P/LP Variants			
102	0	0	1st degree FH	0	0	0	0	0	0	No P/LP Variants			
103	1	2	No family history	0	0	0	0	0	0	No P/LP Variants			
104	0	16	No family history	1	0	0	0	1	1	No P/LP Variants			
105	1	0	No family history	1	0	0	0	1	0	No P/LP Variants			
106	1	1	No family history	1	1	0	0	1	0	No P/LP Variants			
107	0	15	No family history	1	0	0	1	1	0	No P/LP Variants			
108	0	15	No family history	0	1	0	0	0	0	No P/LP Variants			
109	1	15	No family history	0	0	0	0	0	0	No P/LP Variants			

Abbreviations: * = Truncation; del = Deletion; fs = Frame shift; dup = Duplication. All variants are heterozygous, except 1 hemizygous and 1 mitochondrial variant.