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Rare variant mutations identified in pediatric patients with dilated cardiomyopathy

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Abstract

Dilated cardiomyopathy (DCM) in infants and children can be partially explained by genetic cause but the catalogue of known genes is limited. We reviewed our database of 41 cases diagnosed with DCM before 18 years of age who underwent detailed clinical and genetic evaluation, and summarize here the evidence for mutations causing DCM in these cases from 15 genes (PSEN1, PSEN2, CSRP3, LBD3, MYH7, SCN5A, TCAP, TNNT2, LMNA, MYBPC3, MYH6, TNNC1, TNNI3, TPM1, and *RBM20)*. Thirty-five of the 41 pediatric cases had relatives with adult-onset DCM. More males (66%) were found among children diagnosed after 1 year of age with DCM. Nineteen mutations in 9 genes were identified among 15 out of 41 patients; 3 patients (diagnosed at ages 2 weeks, 9 and 13 years) had multiple mutations. Of the 19 mutations identified in 12 families, mutations in *TPM1* (32%) and *TNNT2* (21%) were the most commonly found. Of the 6 patients diagnosed before 1 year of age, 3 had mutations in *TPM1* (including a set of identical twins), 1 in *TNNT2*, 1 in *MYH7*, and 1 with multiple mutations (*MYH7* and *TNNC1*). Most DCM was accompanied by advanced heart failure and need for cardiac transplantation. We conclude that in some cases pediatric DCM has a genetic basis, which is complicated by allelic and locus heterogeneity as seen in adult-onset DCM. We suggest that future prospective comprehensive family-based genetic studies of pediatric DCM are indicated to further define mutation frequencies in known genes and to discover novel genetic cause.

Keywords

cardiomyopathy; death; sudden; genes; pediatrics; children

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Conflict of Interest: None

Introduction

Dilated cardiomyopathy (DCM) occurs in infants and children (<18 years old) and is defined, as in adults, by left ventricular enlargement (LVE) and systolic dysfunction. Reported incidence rates for pediatric DCM range from 0.34 to 3.8 cases/100,000 per year, lower than those for adult-onset cases (5.5 cases/100,000) [1,2,3]. Higher rates of 8.34/100,000 [3] have been reported in infants (<1 year old) compared to children ages 1 to18 years old, and in boys compared to girls (0.66 *vs.* 0.47/100,000) [2]. Uncovering the etiology of pediatric DCM is difficult because of the marked clinical heterogeneity due to variability in clinical presentation, age at onset (fetal, neonatal, early childhood, and late childhood), and heart failure status [4].

Pediatric DCM has been hypothesized to have a genetic etiology in some cases. However, only a few mutation analyses in case reports and in families with primarily adult-onset DCM have been reported (Table 1). Mutations in 16 genes have been reported in children with idiopathic DCM (IDC) causing familial DCM (FDC) and IDC (sporadic disease) (Table 1). Most reported mutations were in families with multiple affected relatives diagnosed with DCM during childhood or adulthood. Genes for which the same mutations were identified in ≥ 4 affected relatives in the same pedigree include dystrophin (*DMD*), succinate dehydrogenase complex, subunit A, flavoprotein (*SDHA*), α tropomyosin 1 (*TPM1*), and troponin T Type 2 (*TNNT2*) [5,6,7]. In the two largest published pedigrees, the same *SDHA* Gly555Glu mutation was identified in 15 patients between the ages of 32 weeks *in utero* to 10 years of age in a large consanguineous Bedouin tribe [8] and the same *TPM1* Asp230Asn missense mutation was identified in 9 relatives (3 males, 7 females) diagnosed with DCM between ages 5 months to 16 years [6]. DCM gene mutations have been reported in multiple ethnic/geographic populations including non-Hispanic Caucasians, French Canadians, Blacks, Japanese, and Han Chinese (Table 1). In most instances, mutations in pediatric cases were identified through family members of FDC probands with adult-onset DCM. As a result, the literature on genetic mutations in pediatric DCM cases is limited to a few of the investigated mutations, with no comprehensive multigene resequencing studies of pediatric DCM cases published to date.

We undertook a systematic review of our Familial Dilated Cardiomyopathy (FDC) Research Project database [9] designed for family-based genetic studies to identify all pediatric DCM cases and evidence for mutations. In all identified cases, available clinical and molecular genetic data were analyzed.

Methods

FDC Research Project Patient Population

Subjects with IDC (with or without FDC) were enrolled, as described previously [9]. Written informed consent was obtained. A blood sample was obtained for genetic research. Medical and family history was obtained, and a pedigree was constructed. Medical records were obtained to confirm IDC or FDC and assign familial or sporadic status. IDC was defined as left ventricular enlargement with systolic dysfunction, with coronary artery disease, cardiotoxic exposures, and other known causes ruled out [9]. FDC cases were defined as those in which the patient and at least 1 relative had IDC confirmed by medical records or death certificate, regardless of age at onset. IDC, probable FDC was used to classify pedigrees in which family history strongly suggests FDC, however, medical records were not available to confirm additional cases of IDC in the family [9]. Patient information was stored in Progeny, a relational database (Progeny Software, South Bend, IN).

Database Query and Medical Records Review of Pediatric DCM

A database query among 324 whose data were part of the FDC Research Project cohort and who were resequenced for known DCM genes [10-12,13,14] was conducted for DCM cases diagnosed or deceased younger than 18 years of age.

Selection Criteria

Cases were selected if medical records or death certificate indicated a diagnosis of DCM under the age of 18 at the time of enrollment. Those classified as affected with IDC (per criteria below and previously published in detail [9]) and diagnosed or deceased under age 18 were included as a pediatric DCM case. All available medical records in the database were reviewed for onset of disease or death before the age of 18 years, and for cardiovascular data indicating systolic dysfunction (an ejection fraction <50%, or echocardiographically-derived fractional shortening <28-30%) and left ventricular end-diastolic dimension considered dilated for the age, gender and size of the patient.

Genetic Data

Genetic data from comprehensive resequencing studies were available from the families of 41 subjects (across 31 families); all coding exons and near intron/exon boundaries underwent bidirectional capillary-based Sanger sequencing, as described previously [10-12,13,14]. Thirteen cases were resequenced for 15 genes, including PSEN1, PSEN2, MYH7, TNNT2, SCN5A, CSRP3, LBD3, TCAP, LMNA, MYBPC3, MYH6, TPM1, TNNC1, TNNI3, and *RBM20* [10-13,15]. Three cases were resequenced for all genes except for *PSEN1* and *PSEN2*. One case was sequenced for *LMNA*, *PSEN1*, and *PSEN2*. One case was sequenced for *LMNA*, *PSEN2* and tested for a known family mutation in *MYBPC3*. One case was sequenced for *LMNA* only. Four cases were tested for a known DCM mutation in one of these 15 genes identified in a relative. Eighteen cases were not sequenced for genes, but had a relative who was sequenced for all or most of these genes. This included 8 cases that had at least 1 relative with a known gene mutation but were not tested for this family mutation because DNA was not available on the subject, 9 cases had at least 1 relative who was sequenced for 15 genes and no mutations were identified, and 1 case whose relative had been sequenced for all genes except *PSEN1* but no mutations were identified.

Results

Clinical Data

Overall—A search of children diagnosed with DCM in 324 families enrolled in the Familial Dilated Cardiomyopathy Research Project cohort in which at least 1 family member underwent resequencing in our previous publications [10-12,13,14,15] identified 41 cases with DCM in 31 families (Table 2). Four of these cases were apparently sporadic IDC, and 2 further cases were lacking sufficient clinical data to verify family history of FDC, though FDC was likely based on family history intake (termed ‘IDC’ and ‘probable FDC,’ respectively, as previously described [9]). The remaining 35 pediatric cases of DCM were identified within 25 FDC families, including one family with multiple types of cardiomyopathy (two DCM, one arrhythmogenic right ventricular dysplasia/cardiomyopathy – ARVD/C). This group includes a set of female identical twins, a female proband and her two paternal half brothers, a sister pair, a sister and brother pair, two sisters and a male first cousin, two pairs of male 1st cousins and a father-son pair. Overall, more pediatric DCM cases were observed in the FDC Research Project cohort in children (n=35) compared to infants (n=6). Among children > 1 year old, males comprised 66% of identified DCM cases (23 males *vs.* 12 females).

Twenty-two of 25 FDC families had at least 1 adult-onset case in the family, with 45 total adult cases and 25 pediatric cases confirmed by medical records or death certificates. The three remaining FDC families had only pediatric onset cases. Across 22 families with at least 1 adult onset diagnosis of DCM (n=45), the age of onset for adult cases ranged from 18 to 67 years old (median 39 yrs). Age of pediatric diagnoses within these families ranged from 3 months to 17 years, (median 14 yrs). Across all families with pediatric diagnoses (n=31), age at diagnosis ranged from 2 weeks to 17 years (median 11 yrs).

Cases where a mutation was identified in the family—Medical records and/or death certificates were available for 41 pediatric cases, 15 of whom have a known gene mutation [10-12,13,15]. Cardiovascular characteristics of these cases are provided (Table 3). An additional 8 pediatric DCM cases were confirmed with medical records or death certificate among families with a known mutation, however, they did not have DNA available for analysis. Three of these cases were asymptomatic at the time of presentation (ages 7, 12, 14 yrs) having undergone cardiovascular screening based on a family history of DCM. Two cases presented with signs of respiratory distress, one with cough and shortness of breath, and the other with a flu-like illness. Both were found to have DCM after chest x-rays revealed cardiomegaly. Clinical data at the time of presentation in the remaining two cases were not available. Family data are summarized by pedigree below.

Cases where a mutation was not identified in the family—Among 17 pediatric cases in which the proband or family member did not have a mutation identified in the genes sequenced, four were asymptomatic and presented based on FDC screening, and eight had signs of respiratory distress, pneumonia, or viral or other infection. One of these cases has a bilineal history of FDC, with a mutation identified on the maternal side of the family, but no known mutation in any of the 15 genes on the paternal side of the family.

Genetic data

Genetic data were available for 31 families with pediatric cases (24 familial DCM, 4 sporadic, 2 IDC, probable FDC, and 1 with a mixed ARVD/DCM phenotype in the family). A total of 15 of the 31 families with pediatric cases were found to have a mutation in our resequencing studies [10-12,13,15]. Of these, 7 pediatric cases were sequenced for all 15 genes while 3 were sequenced for all genes but *PSEN1* and *PSEN2*. One individual was sequenced for *LMNA*, *PSEN1* and *PSEN2* only and found to carry a *LMNA* mutation. Four additional pediatric cases were found to carry a mutation initially identified in their affected relative who had been sequenced for 13-15 genes (Table 3).

In 12 families, missense mutations in 9 different genes were found in pediatric cases (Table 2, Table 3). Three cases had multiple mutations in different genes (Table 3): both *TNNC1* and *MYH7* mutations were identified in the youngest pediatric case (diagnosed at 2 weeks old); 1 case had a mutation in *TNNT2* and two mutations in *MYH6*; 1 case had mutations in *TNNT2* and *TPM1*. A missense variant (Lys15Asn, chr15:61122126, hg18) in *TPM1* was detected in three pediatric cases in the same family (diagnosed at 8 months, 8 years, and 10 years). A missense variant (Ile92Thr, chr15:61136271, hg18) in *TPM1* was detected in a set of female identical twins diagnosed with DCM in infancy. Mutations in *TNNT2*, *TPM1*, and *MYH7* were found in both FDC and IDC pediatric cases.

Among the remaining 16 families, 6 pediatric cases were sequenced for all 15 genes and no mutation was identified. One pediatric case was a sibling to one of these probands and was not tested. One case was sequenced for *LMNA* only and no mutations were identified. The remaining 8 cases were in families in which an adult relative was sequenced for 14-15 genes and did not carry a mutation; one case was sequenced for all 15 genes except *PSEN1*.

Pedigrees with Pediatric DCM (Table 3)

FDC families with a pediatric case having 1 mutation

A.1: The proband, a non-Hispanic white male, presented at age 15 with shortness of breath initially thought to be pneumonia. He was subsequently diagnosed with heart failure and received a heart transplant 4 months later. The proband was sequenced for *LMNA*, *PSEN1* and *PSEN2* and found to carry a *LMNA* Arg399Cys variant not found in 150 controls; his family pedigree has been published [12,16]. His father, who was diagnosed with DCM at age 25 and subsequently received a heart transplant at age 36, underwent sequencing for 15 genes, all of which were negative for mutations including the *LMNA* mutation found in his son. The proband's mother carried this mutation. Although his mother's cardiovascular evaluation at age 43 was negative, his paternal grandfather, who also carried the *LMNA* variant, required a pacemaker and had a left bundle branch block at age 75 as well as a family history of arrhythmia and cardiomyopathy. Functional studies performed on this variant and clinical evidence from the pedigree [12,16] suggest that the mutation is partially penetrant with later onset, consistent with the lack of cardiovascular findings in the mother in her early 40s. We surmise that the early onset in the proband at 15 years may have been this variant acting in concert with a second paternal mutation, the identity of which is not yet known.

B.1: The proband, a non-Hispanic white male who presented at age 17 with an episode of sudden cardiac death, was revived with cardiopulmonary resuscitation. An implantable cardiac defibrillator was placed. Coronary angiography revealed no coronary disease. A missense *MYBPC3* Ala833Thr variant not seen in 246 controls was detected [13]. This variant was also seen in affected relatives including his father (diagnosed at age 40) and his paternal aunt (diagnosed at age 42).

C.1: The proband, a non-Hispanic white male, presented with chronic cough and failure to thrive, as well as a family history of pediatric DCM. Echocardiographic screening revealed DCM at 1 month old. Coronary angiography was normal. He received a heart transplant at 12 months of age. A missense *MYH7* Glu1619Lys variant not seen in 253 controls was detected [11]. His father was diagnosed with DCM at age 13 months, however, no DNA was available for genetic testing and segregation is unknown. Additional paternal relatives were reported to have DCM by family history, including a paternal aunt and 2 paternal 1st cousins once removed, but medical records are not available to confirm these diagnoses.

D.1: The proband, a non-Hispanic white male, began asymptomatic cardiac screening in childhood due to a family history of FDC. At age 10, his electrocardiogram (ECG) revealed premature ventricular contractions with nonspecific ST-T wave changes, though the patient was asymptomatic. His echocardiogram at age 12 was normal, but repeat echocardiography at age 17 revealed an left ventricular end-diastolic dimension of 78mm and an ejection fraction of 12.5%. He was asymptomatic and was started on carvedilol. The subject's father, diagnosed with DCM at age 32, was sequenced for 15 genes and found to carry a missense *SCN5A* (Arg222Gln) variant absent in 253 controls [11]. This variant segregated with disease in 6 affected individuals in the family, and the pedigree has been previously published [14], including one female diagnosed with peripartum cardiomyopathy.

E.1: The proband, a non-Hispanic white female, presented at 6 years old with acute viral illness and gastroenteritis. A chest x-ray showed an enlarged heart and a subsequent echocardiogram revealed a diagnosis of DCM. She received a heart transplant at 7 years of age. A missense *TNNT2* Arg134Gly variant not seen in 253 controls was detected [7]. Her paternal uncle was subsequently diagnosed with DCM at age 34 after an episode of palpitations and dizziness. Her father underwent cardiac screening based on family history

several years later at age 34 and was also diagnosed with DCM. The mutation segregates with disease in this family.

FDC families with multiple related pediatric cases sharing the same mutation

F.1, F.2, F.3: The proband, a non-Hispanic white female was healthy until 2 months when she presented with progressive difficulty breathing. Chest x-ray revealed cardiomegaly and an echocardiogram revealed DCM. She received a heart transplant at 18 months. The proband was sequenced for 15 genes and found to have a heterozygous missense *TPM1* Lys15Asn variant not seen in 246 controls [13]. Her paternal half brothers, ages 8 and 10, who were asymptomatic, underwent cardiovascular screening and were diagnosed with DCM. The older sibling was placed on angiotensin converting enzyme inhibitors and his echocardiographic findings improved. The mutation was present in both siblings, as well as their father, who had an ECG at age 39, revealing a left anterior hemiblock and slow R wave progression. He underwent an echocardiogram at age 46 which revealed left ventricular hypertrophy with systolic function at the lower limits of normal.

G.1,G.2: The proband, a non-Hispanic white female identical twin, born at 34 weeks gestation, presented at 3 months of age with unconsolable crying and palor, and upon arrival in the emergency room was found to be in cardiorespiratory shock. She had a reported episode of agitation and pale appearance 5-6 weeks prior to diagnosis, and a 2 week history of poor feeding and shortness of breath. Her identical twin subsequently underwent cardiovascular screening and was diagnosed with DCM. The proband and her twin underwent heart transplants, at 5 months and 8 months, respectively. The proband was sequenced for 13 genes (excluding *PSEN1* and *PSEN2*) and found to be heterozygous for a missense *TPM1* Ile92Thr variant, which was also observed in her twin sister [13]. Their mother and maternal uncle both had adult-onset DCM diagnosed at ages 43 and 34, respectively, and were found to carry this variant. Their maternal grandmother, who also carried this variant, developed non-ischemic DCM at age 59 post doxorubicin chemotherapy for lymphoma. The variant segregates with disease in this family.

FDC families with pediatric cases having multiple mutations

H.1: The proband, a non-Hispanic white female, was diagnosed with asymptomatic DCM after routine cardiovascular screening due to family history of DCM at the age of 9 years. Three missense variants (*TNNT2* Lys210del; *MYH6* Ile275Asn; *MYH6* Arg1502Gln) not seen in 253, 246 and 246 controls, respectively, were detected in the proband [11,13]. Her sister was also diagnosed with asymptomatic DCM on cardiac screening due to maternal family history at age 12.

IDC families with pediatric cases having multiple mutations

I.1: The proband, a non-Hispanic Black male, was diagnosed at age 13 years with DCM after a four day history of respiratory distress and elevated resting heart rates, low energy and exercise intolerance. Coronary angiography was normal. His ejection fraction was 7% and left ventricular end-diastolic dimension was 70 mm. At age 13 he required a left ventricular assist device and subsequently received a heart transplant. Two missense variants (*TNNT2* Glu244Asp; *TPM1* Ala277Val) not seen in 169 and 167 African American controls, respectively, were detected in the proband [11,13]. His mother underwent echocardiographic screening at age 39 that was normal; she had nonspecific ST-T wave changes on ECG. No further clinical or genetic data are available.

J.1: The proband, a non-Hispanic white male, was hospitalized with heart failure at 2 weeks of age and was diagnosed with congenital DCM. He received medical therapy, but developed heart failure at age 14, and received a heart transplant at age 15. Two missense

variants (*TNNC1* Tyr5Cis and *MYH7* Arg1045Cys) not seen in 246 controls and 253 controls, respectively, were detected in the proband [11,13]. He was an only child. His mother, who was clinically unaffected (negative echocardiogram and ECG at age 47), was negative for both variants. No other clinical or genetic data are available for this family.

IDC cases with 1 mutation

K.1: The proband, a non-Hispanic white male, presented at 18 months of age with an acute viral illness. His mother, father and 3 year old brother also had a similar illness, from which they recovered within 1 week. The proband's symptoms, however, persisted for several weeks. Chest x-ray revealed cardiomegaly. He was diagnosed with DCM with an ejection fraction of 20% and a severely enlarged left ventricle. He underwent heart transplant at 6 years, and according to the family died at age 11 from heart failure and enlargement of his transplanted heart. A missense *TNNI3* Asp180Gly variant not seen in 246 controls was detected [13]. Additional relatives are reportedly affected with adult-onset DCM in this family, including his father, paternal aunt, paternal grandmother, and paternal 1st cousin once removed, but DNA and medical records are not available for these family members.

L .1: The proband, a non-Hispanic white female was diagnosed at 6 months of age with post-viral dilated cardiomyopathy. She was treated medically, but progressive heart failure occurred necessitating heart transplant at age 12. A missense *TNNT2* Arg205Trp variant not seen in 253 controls was detected [7,11]. No other relatives were available for clinical data or mutation screening.

Additional FDC families with known mutations and a pediatric DCM case

Our database search revealed an additional 3 pedigrees with a known mutation in a DCM gene in which pediatric DCM cases were confirmed based on medical or death certificate records, however, DNA samples were not available.

Pedigree 1—The proband, a non-Hispanic white female, was diagnosed with DCM at age 39 soon after her daughter's diagnosis of IDC. Her daughter had an episode of syncope at age 13 and was subsequently diagnosed with DCM on echocardiogram. She had a heart transplant at age 14. The proband was resequenced for 15 genes and found to be heterozygous for a missense *TPM1 Ala239Thr* variant not found in 246 controls [13]. She has a son who began preventive asymptomatic cardiac screening at age 2, and subsequently was diagnosed with asymptomatic DCM on echocardiogram at age 7. DNA from additional relatives was not available.

Pedigree 2—The proband, a non-Hispanic white female, was diagnosed with asymptomatic DCM at age 43 when she underwent cardiac screening based on her family history of FDC. She was sequenced for 15 genes and found to be heterozygous for a missense *RBM20 Arg636Cys* variant not found in 450 controls [15]. This variant segregated with disease in her son, who was diagnosed with DCM at age 23 on asymptomatic cardiovascular screening due to family history of DCM. Her sister died at age 23 with a history of peripartum cardiomyopathy. This sister had 2 daughters, the older of which presented with coughing and shortness of breath, and underwent heart transplant at age 16; her sister subsequently underwent transplant for DCM at age 14. DNA from deceased relatives was not available. The pedigree has been previously published (Pedigree D, [15]).

Pedigree 3—The proband, a non-Hispanic white female, was diagnosed with DCM at age 59, and was sequenced for 15 genes. He was found to be heterozygous for a missense *TNNT2* lys210del variant not found in 253 controls [7,11]. This variant segregated with disease in her male maternal 1st cousin, diagnosed with DCM at age 52. The proband's

brother was diagnosed with DCM and died at age 16 in advanced heart failure; another male maternal 1st cousin died at age 12 months with DCM at autopsy. DNA from the deceased relatives was not available; this pedigree has been previously published [17].

Discussion

From our database designed for genetic studies of familial dilated cardiomyopathy, we now report the cases of dilated cardiomyopathy with onset before 18 years of age. Forty-one pediatric cases were identified within 31 families, of which 18 individuals had undergone sequencing for known DCM genes and 4 had undergone testing for a known family mutation. Of these 31 families, one or more mutations likely causative of disease were identified in 9 genes from 15 families. Of the mutations identified in these families, mutations in *TPM1* (32%) and *TNNT2* (21%) were the most commonly found. One or more mutations were identified in *LMNA, MYBPC3, MYH6, MYH7, SCN5A, and* TNNC1 and TNNI3. These data convincingly show that a proportion of childhood cardiomyopathy may be accounted for by genetic cause, and more specifically support and extend previous reports showing that nonsynonymous rare variants, predominantly in sarcomeric genes, are causative of pediatric DCM.

Notably, 17 of the 19 mutations (except for two, one each in *LMNA* and *SCN5A*) were identified in 7 genes that encode proteins of the cardiac sarcomere, suggesting that specific sarcomeric mutations, as observed here, may be associated with early onset, aggressive disease. The one case of the *LMNA* mutation was observed in a proband with a presumptive second, yet unidentified, genetic variant from his father who had FDC. We also note that three cases had multiple mutations, which may also explain early onset disease. Because we only sequenced 15 of the more than 30 genes shown in association with DCM, it is possible that other cases of pediatric DCM also harbored multiple mutations, either within previously described DCM genes or within novel genes not yet associated with DCM.

In agreement with reported estimates in other pediatric cohorts, from our database we observed more males (66%) compared to females among cases with onset between 1 to 18 years of age. Since only 6 cases with onset before 1 year old were identified (including a set of identical twins), we are unable to provide reliable estimates of sex differences among infants. Although it has been reported elsewhere [3,18,19], we did not observe higher overall rates of DCM among infants compared to children ages 1-17 in the FDC cohort.

In this cohort, DCM diagnosis in pediatric cases with a known disease-associated gene mutation was based on cardiovascular screening largely of children presenting with acute viral illness, respiratory distress, or failure to thrive. Five of the cases (33%) with mutations were identified through routine cardiovascular screening of asymptomatic individuals with a known family history of DCM. Of the familial cases, all but three pediatric cases were identified in FDC pedigrees with adult-onset DCM in other relatives.

Future research opportunities

The remaining genetic cause, if present in these children, remains unknown, but could be accounted for by other known DCM genes that we did not sequence, other genes not yet reported in association with DCM, or mutations within these genes not detectable with resequencing techniques, such as copy number variation and other genetic mechanisms. We also note that the high degree of genetic heterogeneity of DCM suggests many genes that have not been previously associated with DCM, perhaps even more so in pediatric DCM, may be found to be causative of disease. Larger, prospectively conducted family-based studies directed at all ages of pediatric DCM, in the context of familial and sporadic disease,

coupled with genome-wide sequencing approaches, will be needed to further define the genetics of pediatric DCM.

Copy number variations, defined as the loss or gain of regions of DNA greater than 1kb in size, are usually missed by standard DNA sequencing approaches. To date, large deletions (ranging ~2-400 kb) in the known DCM genes *DMD, EYA4* and *LMNA* have been identified in patients presenting solely with DCM [21,22,23]. The latest high resolution DNA microarrays will allow discovery of structural variants at a genome-wide level, allowing a comprehensive assessment of the contribution of copy number variation that may be particularly relevant in pediatric as well as adult-onset DCM.

Limitations

The principal limitation of this ≥15 year study is that it has primarily recruited from adult cardiology settings. However, the study was designed to accept referrals of DCM probands of all ages, and has previously published in the pediatric cardiology literature [20], which has enhanced our pediatric referrals. Nevertheless, the nature of this study design limits the generalizability of any incidence or mutation estimates to a population level. We also note that because our principal focus historically had been to identify patients with DCM in families, it is not surprising that the majority of pediatric cases we identified were familial, a focus that may also have enriched this cohort for those with heritable genetic disease. Nevertheless, the identification of mutations in two sporadic cases of pediatric DCM in genes also seen in familial cases suggests the possibility of shared genetic etiology for both familial and sporadic forms of the disease. Our resequencing data were limited to selected genes known to cause DCM in all cases regardless of age; therefore it is possible that genes more relevant to early-onset pediatric DCM were missed. In some FDC pedigrees, only the mutation identified in the proband was sequenced in other affected relatives, including some of these pediatric DCM cases, so that additional mutations relevant for this study may have been missed.

Conclusions and implications for clinicians

As has been previously known, rare variant mutations in key myocardial proteins cause DCM in pediatric patients in the settings of sporadic IDC and FDC. These data extend the prior literature, and emphasize the importance of genetic cause in the differential diagnosis of DCM found in the neonatal, infant and childhood periods, and the application of genetic guidelines [46] developed for DCM in adults and children.

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Table 1

Genetic Mutations in Pediatric Dilated Cardiomyopathy by Other Investigators

Gene	Mutation	Locus	OMIM	Gene Product	Age range	Gender	Ethnic groups	FDC/IDC[a]	Associated syndromes	Refer-ences
ANKRD1	Pro105Ser	10q23.31	609599	Ankyrin repeat domain 1	15 y	n/a	Non-Hispanic White	FDC	---	24
CHRM2	Cys176Trp	7q31-q35	118493	Cholinergic receptor, muscarinic 2	16-17 y	2M	Han Chinese	FDC	---	25
DSG2	Val919Gly	18q12.1-q12.2	612877	Desmoglein 2	<18 y	M	German white	FDC	---	26
DMD	IVS1+5G>A	Xp21.2	302045	Dystrophin	13 y	M	Japanese	n/a	---	27
	IVS1 +1 G>T				<18 y	4M	French Canadian	FDC	Barth syndrome	28
LMNA	FS 321	1q21.2	115200	Lamin A/C	4 y	F	Italian	FDC	EDMD[b], LGMD[c], CMT[d]	29
	Arg377Leu				16 y	M	n/a	n/a	--	30
	Arg541Lys				13 y	M	n/a	n/a	--	30
	Nonsense mutation, R321stop				16 y	F	n/a	n/a	--	31
MYH7	Phe764Leu	14q12	160760	β-myosin heavy chain	Birth - 11 y	M	Non-Hispanic White	FDC	---	32
	Ser532Pro				2 - 18 y		Non-Hispanic White	FDC	---	32
	Lys637Glu				13 y	F	Non-Hispanic White	FDC	---	32
	Ser642Leu				18 y	M	n/a	FDC	---	32
RBM20	Pro638Leu	10q25.2	613171	RNA binding motif protein 20	3 -17 y	M	German white	FDC	---	33
	Arg636Ser				17 y	F	Norwegian white	FDC	SMA[e]	33

Gene	Mutation	Locus	OMIM	Gene Product	Age range	Gender	Ethnic groups	FDC/IDC[a]	Associated syndromes	References
SDHA	Gly555Glu	5p15	600857	Succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	32 w gestation - 8 m	8M:7F	Bedouin	FDC	Barth Syndrome; Fukuyama-type congenital muscular dystrophy;LGMD;Walker-Warburg syndrome	34
SG	---	17q12-q21.33	600119	Sarcoglycan, Alpha; SGCA	12 y	M	n/a	IDC	β-Sarcoglycanopathy; early-onset LGMD;5 sarcoglycanopathy	35
TPM1	D230N	15q22.1	191010	Tropo-myosin 1	10 w - 16 y	3M:7 F	Non-Hispanic White	FDC	---	6
TTN	C-terminal titin (TTN) deletions	2q31	604145	Titin	5 - 16 y	n/a	Sudanese/Moroccan	FDC	---	36
TNNC1	Gly159Asp	3p21.3-p14.3	191040	Troponin C type 1	3 y	M	n/a	FDC	---	37
	Gly159Arg				< 18 y	F	n/a	FDC	---	38
	Gln50Arg				16 m	F	n/a	FDC	---	39
TNNI3	Lys36Gln	19q13.4	611880	Troponin I type 3	6 - 15 y	M	n/a	FDC	---	40
TNNT2	Arg134Gly	1q32	601494	Troponin T type 2	12, 6 y	1M:1F	Non-Hispanic White	FDC	---	41
	Arg151Cys				6 y	F	Non-Hispanic White	IDC	---	41
	Arg159Gln				5 m	F	Non-Hispanic White	IDC	---	41
	Ala171Ser				3 - 17 y	4M: 6F	n/a	FDC	---	41
	Lys210del				1-16 y	3F:4M	Non-Hispanic White	FDC	---	41
	Glu244Asp				13 y	M	Non-Hispanic White	IDC	---	41
	Glu96Lys				5 m	F	n/a	FDC	---	

Gene	Mutation	Locus	OMIM	Gene Product	Age range	Gender	Ethnic groups	FDC/IDC[a]	Associated syndromes	References
	Arg141Trp				1.5 - 2 m	2M	Non-Hispanic White	FDC/IDC		41
	Arg205Leu				16 y	F	n/a	FDC	---	42
	Arg141Trp				1 - 17y	1M:5F	n/a	FDC	---	43
TRNE	T14709C	mtDNA	590025	Mitochondrially encoded tRNA glutamic acid	6 w	F	n/a	IDC	---	44
UBR1	IVS26 + 5G>A	15q15-q21.1	243800	Ubiquitin protein ligase E3 component n-recognin 1	8 m	F	Turkish	n/a	Johanson-Blizzard syndrome	45

Abbreviations throughout table: CMT, Charcot-Marie Tooth type; EDMD, Emery-Dreifuss muscular dystrophy; FDC, Familial Dilated Cardiomyopathy; IDC, Idiopathic dilated cardiomyopathy; LGMD, Limb-girdle muscular dystrophy; SMA, Spinal Muscular Atrophy

Table 2

Demographics and Mutation Status of Pediatric Cases and Their Families (this report)

	All cases	Infants[a] (<1 yr old)	Children (>1 yr old)
Age, gender, race, ethnicity			
No. of cases	41	6	35
Gender			
Male	25	2	23
Female	16	4	12
Race and ethnicity			
Non-Hispanic white	34	6	28
Hispanic white	2	0	2
Non-Hispanic black	2	0	2
Non-Hispanic American Indian/Alaska Native	1	0	1
Non-Hispanic Asian	2	0	2
Unknown			
Age at diagnosis (median yrs)	11	0.45	13
Familial or sporadic disease			
Total Families	31	6	28
FDC	24	4	22
IDC, probable FDC	2	0	2
IDC	4	2	2
Cardiomyopathy, multiple types[b]	1	0	1
Pediatric mutation status			
Number of families with mutation identified	15	5	10
Number of families with mutation identified in a pediatric case	12	5	7
Pediatric cases with a mutation	15	6	9
Pediatric cases with no mutation	1[c]	-	1
Pediatric cases not sequenced	5	-	5
Number of families with pediatric case without DNA sequencing	3	-	3
Number of families with no mutation identified	16	-	16
Families with pediatric cases sequenced for genetic mutations[d]	7	-	7
Additional pediatric cases within families	1	-	1
Number of families with adult cases sequenced for genetic mutations	9	-	9

[a] 6 total infant diagnoses, 2 of which had at least 1 sibling diagnosed between 1-18yrs. 2 identical twins, 2 IDC)

[b] This family had 2 members with DCM and 1 with ARVD/C

[c] This person has a bilineal history of DCM. Both parents have been sequenced for 15 genes.

[d] All probands sequenced for 15 genes, except 1 (*LMNA* only)

Table 3

Clinical Characteristics of Pediatric DCM Cases with DCM Mutations in this Report

Subject	Gene/Mutation	Sequenced genes[a]	Age at diagnosis	FDC /IDC	Number affected in family (age at onset range, median)	Segregates in family	Gender	Clinical presentation at diagnosis	ECG/Arrhythmia	Echo LVIDd,mm	Systolic Function, EF or FS (%)	Age at LVAD, ICD, PCM	Age at transplant(s)	Age and Vital Status at last point of contact; (cause of death)
FDC cases with 1 mutation														
A.1	***LMNA*** (Arg399Cys)	*LMNA, PS1, PS2*	15y	FDC	2 (15y-25y; 20y)	No	M	Acute illness (SOB; rule out pneumonia)	Sinus tach, NSSTT wave changes	73mm	22.5, EF	LVAD ,16y	16y	Alive at 21 y
B.1	***MYBPC3*** (Ala833Thr)	13 genes (no *PS1, PS2*)	17y	FDC	6 (14y-44y; 31y)	Yes[b]	M	SCD	NSR	62mm	10, EF	ICD, 17y	---	Alive at 17y
C.1	***MYH7*** (Glu1619Lys)	15 genes	1mths	FDC	2 (1mths-13mths; 7mths)	Unknown	M	Asymptomatic[c]	sinus tach; marked ST depression consistent with subendocardial injury; LAD	42mm	17, FS	---	12mths	Alive at age 7y
D.1	***SCN5A*** (Arg222Gln)	family mutation	17y	FDC	6 (17y-51y; 26y)	Yes	M	Asymptomatic	NSCD (at 9y); LBBB (at 16y)	78mm	12.5, EF	---	---	Alive at 17y
E.1	***TNNT2*** (Arg134Gly)	15 genes	6y	FDC	2 (6-23y; 15y)	Yes	F	Acute illness (Viral; rule out pneumonia)	NSVT, PVCs	57.5mm	19, EF	---	7y	Alive at 17y
FDC families with multiple related pediatric cases sharing the same mutation														
F.1	***TPM1*** (Lys15Asn)	15 genes	2mths	FDC	3 (2mths-10y; 8y)	Yes	F	Acute illness (rule out viral pneumonia)	NSR; LVH	35mm	26, EF	---	18mths	Alive at 3y
F.2	***TPM1*** (Lys15Asn)	family mutation	10y	FDC	same as above	Yes	M	Asymptomatic	Sinus Arrhythmia	49mm	42, EF	---	---	Alive at 13y
F.3	***TPM1*** (Lys15Asn)	family mutation	8y	FDC	same as above	Yes	M	Asymptomatic	NSR	47mm	50, EF	---	---	Alive at 11y
G.1	***TPM1*** (Ile92Thr)	13 genes (no *PS1, PS2*)	3mths	FDC	4 (3mths-43y; 17y)	Yes	F	FTT (poor feeding, SOB); shock	---	LVE	22.5, EF	---	5mths	Alive at 2y
G.2	***TPM1*** (Ile92Thr)	family mutation	9mths	FDC	same as above	Yes	F	FTT (identical twin diagnosed with DCM)	---	---	---	---	8mths	Alive at 2y
FDC families with pediatric cases having multiple mutations														
H.1	***TNNT2*** (Lys210del) ***MYH6*** (Ile275Asn) ***MYH6*** (Arg1502Gln)	15 genes	9y	FDC	3 (9y-16y; 12y)	Unknown Unknown Unknown	F	Asymptomatic	---	55mm (age 9); 52mm (age 12)	34, FS (at 9y); 24 FS (at 12y)	---	---	Alive at 24y
Pediatric IDC cases having multiple mutations														

Subject	Gene/Mutation	Sequenced genes[a]	Age at diagnosis	FDC /IDC	Number affected in family (age at onset range, median)	Segregates in family	Gender	Clinical presentation at diagnosis	ECG/Arrhythmia	Echo LVIDd,mm	Systolic Function, EF or FS (%)	Age at LVAD, ICD, PCM	Age at transplant(s)	Age and Vital Status at last point of contact; (cause of death)
I.1[d]	***TNNT2*** (Glu244Asp) ***TPM1*** (Ala277Val)	15 genes	13y	IDC	1 (13y)	Unknown Unknown	M	acute illness (respiratory distress)	LVH, NSSTT, Sinus tach	70mm	7, EF	LVAD, 13y	13	Alive at 13y
J.1	***TNNC1*** (Tyr5His) ***MYH7*** (Arg1045Cys)	15 genes	2wks	IDC	1 (2wks)	Unknown Unknown	M	FTT; HF	Biatrial enlargement, possible RVH	72mm	24, EF	---	15y, 22y	Alive at 27y
Pediatric IDC cases with 1 mutation														
K.1	***TNNI3*** (Asp180Gly)	15 genes	18mths	IDC, Probable FDC	1 (18mths)[e]	Unknown	M	Acute illness (Viral; rule out pneumonia)	NSR	"severely enlarged" at time of transplant	20, EF[f]	---	6y	Died at 11y, (donor heart failure)
L.1	***TNNT2*** (Arg205Trp)	13 genes (no *PS1*, *PS2*)	6mths	IDC	1 (6mths)	Yes	F	Acute illness (Viral; rule out pneumonia)	---	78mm (at 12y)	18, FS (at 12 y)	---	12y	Alive at 19y

Abbreviations throughout table: ECG, electrocardiogram; EF, ejection fraction; FDC, familial dilated cardiomyopathy; FS, fractional shortening; FTT, failure to thrive; HF, heart failure; ICD, implantable cardiac defibrillator; IDC, idiopathic dilated cardiomyopathy; LAD, left axis deviation; LBBB, left bundle branch block; LMNA, Lamin A/C; LVAD, left ventricular assist device; LVE, left ventricular enlargement; LVH, left ventricular hypertrophy; LVIDD, left ventricular end-diastolic dimension in diastole; mths, months old; NSCD, non-specific conduction delay; NSR, normal sinus rhythm; NSSTT, nonspecific ST-T wave changes; NSVT, nonsustained ventricular tachycardia; PCM, pacemaker; PS1, presinilin-1; PS2, presinilin-2; PVCs, multiple premature ventricular contractions; RVH, right ventricular hypertrophy; SCD, sudden cardiac death; SOB, shortness of breath; wks, weeks old; y, years old

[a] The number of genes screened for the individual; 'family mutation' denotes a single mutation identified in a relative who was sequenced for all or nearly all of the 15 genes (see methods).

[b] One additional relative, diagnosed age 14 who does not carry the mutation, however this relative has bilineal DCM (see Results).

[c] Asymptomatic means cardiac screening performed based on family history of IDC/FDC

[d] Not Hispanic, African American. The remainder of thes subjects are non-Hispanic White.

[e] 3 additional individuals reported adult-onset DCM in this family, medical records & DNA samples were not available.

[f] This ejection fraction was by the mother's report; medical records were not available.