ISSN: 2458-8989

Natural and Engineering Sciences

NESciences, 2027, 12 (1): 15-28 doi: 10.28978/nesciences.271002

Genetic and Molecular Characteristics of Familial Dilated Cardiomyopathy in Children: A Case Series

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Abstract

Background. Dilated cardiomyopathy (DCM) is an important cause of heart failure in children and may have a genetic basis, particularly in cases with early disease onset and a positive family history. Genetic heterogeneity may contribute to differences in clinical presentation and disease severity.
Objective. To describe the clinical, laboratory, echocardiographic, radiological, and genetic characteristics of three pediatric cases with familial and genetically determined dilated cardiomyopathy.
Case Series. Three children aged 6–13 years with severe dilated cardiomyopathy were retrospectively evaluated. Clinical assessment, electrocardiography, echocardiography, laboratory investigations, chest radiography, and next-generation sequencing-based genetic analysis were performed. All patients demonstrated progressive heart failure, reduced exercise tolerance, growth retardation, and marked left ventricular systolic dysfunction. Echocardiography showed severe left ventricular dilatation and reduced ejection fraction ranging from 22% to 23%. NT-proBNP levels were elevated in all cases, reaching 6930 pg/mL in one patient. A heterozygous splice-site variant in the FLNC gene,

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c.4737+1G>T, was identified in all three patients and was classified as likely pathogenic. Additional rare variants of uncertain significance were detected in TNNI3K, MYBPC3, MAP2K1, and RBCK1, which may potentially contribute to phenotypic variability.
Conclusion. These pediatric cases demonstrate severe early-onset DCM associated with a likely pathogenic Filamin C (FLNC) splice-site variant and additional rare genetic variants. The findings support the value of comprehensive genetic evaluation and family-based assessment in children with early-onset DCM and suggest that genetic heterogeneity may contribute to differences in clinical severity.

Keywords
Dilated cardiomyopathy; Pediatric cardiology; Filamin C; Genetic testing; Whole-exome sequencing; Familial cardiomyopathy; Sudden cardiac death; Cardiomyopathy-associated genes.

Received: 21/06/2026, Revised: 25/07/2026, Accepted: 19/08/2026, Available Online: 16/09/2026

Introduction

Dilated cardiomyopathy (DCM) is an important cause of heart failure in children and is characterized by left ventricular dilatation and impaired systolic function. Pediatric DCM is associated with substantial morbidity and mortality, particularly when the disease develops at an early age or occurs in the context of a familial predisposition (Nie *et al.*, 2020; Burykina *et al.*, 2025).
The incidence of pediatric DCM has been estimated at approximately 0.5–0.8 cases per 100,000 children per year. Clinical outcomes vary considerably depending on disease etiology, age at onset, severity of ventricular dysfunction, and associated genetic abnormalities (Pappritz *et al.*, 2022; Malinow *et al*., 2024).
In recent years, advances in cardiovascular genetics and next-generation sequencing (NGS) have substantially improved the identification of genetic causes of cardiomyopathy (Xiao et al., 2020; Ware et al., 2021). Genetic testing is an important component of evaluating pediatric patients with suspected heritable cardiovascular diseases and can help guide clinical management and family risk assessment (Landstrom *et al*., 2021).
A considerable proportion of DCM cases are associated with pathogenic or potentially disease-associated genetic variants (Bagnall *et al.*, 2016; Muñoz *et al*., 2021; Wilsbacher, 2020). Frequently implicated genes include TTN, LMNA, MYH7, DSP, BAG3, and TNNT2, which encode proteins involved in sarcomere structure, cytoskeletal organization, and nuclear envelope function (Avery *et al*., 2021; Takacs *et al.*, 2024; Sengupta *et al.*, 2022).
Genotype–phenotype relationships in DCM are complex. Variants in genes such as LMNA and DSP have been associated with conduction abnormalities, ventricular arrhythmias, and increased risk of sudden cardiac death, whereas variants affecting sarcomeric and cytoskeletal proteins may predominantly manifest as ventricular dilatation and systolic dysfunction (Crasto *et al*., 2020; McKenna and Judge, 2021; Diller *et al*., 2021).
Truncating variants in TTN have also been associated with an increased risk of early arrhythmias in patients with dilated cardiomyopathy (Tayal et al., 2017).
Familial clustering is an important feature of inherited cardiomyopathies. Identification of a familial genetic variant may facilitate genetic counseling, clinical surveillance, and targeted testing of relatives (Lee *et al*., 2017; Aonuma *et al.*, 2022). Current recommendations emphasize the role of genetic evaluation in patients with suspected inherited cardiomyopathy and in appropriate family members (Verdonschot *et al.*, 2026; Arbelo *et al.*, 2023).
Pediatric DCM may differ from adult-onset disease in terms of age at presentation, clinical progression, and genetic background (Verdonschot *et al.*, 2020). Early-onset disease with severe ventricular dysfunction and a positive family history should therefore raise suspicion of an inherited cardiomyopathy and may warrant comprehensive molecular investigation (Fernlund *et al*., 2020; Roest *et al*., 2020).
Despite advances in genetic diagnostics, data describing the molecular characteristics of pediatric familial DCM in Central Asian populations remain limited. Regional clinical and genetic data are important for improving recognition of inherited cardiomyopathies and for developing appropriate approaches to family screening and genetic counseling (Ware and Cook, 2018; Khan *et al*., 2022).
The identification of rare variants of uncertain significance (VUS) may further complicate genetic interpretation (Chen *et al.*, 2021). Although such variants cannot be considered independently

diagnostic, their presence may provide hypotheses for future functional and segregation studies (Weldy and Ashley, 2021; Ismail *et al.*, 2024). Interpretation of genetic variants should therefore follow established criteria, including the recommendations of the American College of Medical Genetics and Genomics (Harrison *et al.*, 2019; Vasilescu *et al*., 2018). The genetic evaluation of pediatric DCM presents several challenges because the clinical manifestations of the disease may overlap with those of other cardiac conditions, while the underlying molecular causes can vary between patients. The interpretation of genetic findings therefore requires consideration of the clinical phenotype, family history, and evidence supporting the classification of each identified variant. Although genetic testing can help identify potentially relevant molecular changes, the detection of a rare variant does not necessarily establish its role in disease development.

Filamin C (FLNC) is of particular interest in the investigation of inherited cardiomyopathies the protein contributes to the structural organization of cardiac muscle cells. Published research has described associations between FLNC variants and different cardiomyopathic phenotypes, including dilated and arrhythmogenic forms (Marchetti *et al.*, 2026). These observations provide a scientific basis for investigating FLNC in patients with suspected familial DCM. Nevertheless, the clinical implications of an individual FLNC variant must be assessed using the available genetic evidence rather than inferred solely from the gene in which it occurs.

Another important consideration is the interpretation of additional variants identified during genetic testing. Variants of uncertain significance may be detected alongside a potentially disease-associated finding, but their contribution to the clinical presentation remains unresolved unless further evidence becomes available. Their interpretation may require additional clinical information, family segregation studies, or functional investigations, depending on the circumstances. Distinguishing established findings from uncertain observations is essential to avoid assigning an unsupported genetic explanation to the patient's condition.

These considerations are particularly relevant in children with early-onset DCM and a family history of cardiac disease or premature death. Combining clinical assessment with molecular analysis can provide a more complete description of the affected patients and help identify questions for further investigation. However, the significance of genetic findings must remain proportionate to the evidence available, especially in small descriptive studies where the number of patients limits the conclusions that can be drawn.

The aim of this study was to describe the clinical, laboratory, echocardiographic, radiological, and genetic characteristics of three pediatric patients with familial and genetically determined dilated cardiomyopathy, with particular attention to the identification of potentially disease-associated genetic variants.

2. Materials and Methods

2.1. Study design and patients

This retrospective descriptive case series included three pediatric patients diagnosed with dilated cardiomyopathy. The patients were evaluated at tertiary-level pediatric cardiology centers in Uzbekistan.

Patients were included based on the presence of left ventricular dilatation, reduced systolic function, and clinical features compatible with DCM. Secondary causes of cardiomyopathy, including congenital heart disease, myocarditis, metabolic and endocrine disorders, and major structural cardiac abnormalities, were considered during the diagnostic evaluation.

DCM was defined as left ventricular dilatation accompanied by reduced left ventricular ejection fraction in the absence of abnormal loading conditions.

The patients were 6–13 years of age at the time of evaluation. Detailed medical histories, including family history of cardiomyopathy, heart failure, arrhythmias, and premature or sudden cardiac death, were obtained.

2.2. Clinical assessment

A comprehensive clinical examination was performed in all patients. The assessment included evaluation of dyspnea, fatigue, syncope, exercise intolerance, appetite, growth and nutritional status, cyanosis, tachycardia, hepatomegaly, peripheral edema, and other signs of chronic heart failure.

Particular attention was given to previous infections and other medical conditions that preceded the onset of cardiac symptoms.

2.3. Electrocardiography and Holter monitoring

Standard 12-lead electrocardiography was performed in all patients. The analysis included cardiac rhythm, heart rate, conduction intervals, QRS duration, ventricular hypertrophy patterns, ST–T changes, and arrhythmias.

Twenty-four-hour Holter monitoring was performed when clinically indicated to identify transient or intermittent rhythm abnormalities, including ventricular extrasystoles and other conduction or rhythm disturbances.

2.4. Echocardiographic assessment

Transthoracic echocardiography was performed using standard pediatric echocardiographic views, including parasternal long-axis and short-axis, apical four-chamber, and subcostal views.

The following parameters were evaluated:

- left ventricular end-diastolic diameter (LVEDD);
- left ventricular end-systolic diameter (LVESD);
- left ventricular ejection fraction (LVEF);
- fractional shortening;
- left atrial dimensions;
- mitral regurgitation;
- segmental and global ventricular wall motion;
- pericardial effusion;
- intracardiac thrombi.

Left ventricular dimensions were interpreted according to age- and body-surface-area-adjusted pediatric reference values.

2.5. Laboratory investigations

Laboratory assessment included complete blood count, serum biochemical parameters, cardiac biomarkers, and markers of heart failure.

The following parameters were assessed:

- hemoglobin;
- leukocyte and platelet counts;
- alanine aminotransferase (ALT);
- aspartate aminotransferase (AST);
- creatine kinase-MB (CK-MB);
- lactate dehydrogenase (LDH);
- troponin I;
- NT-proBNP;
- C-reactive protein (CRP);
- serum electrolytes;
- lactate.

2.6. Genetic analysis

Peripheral blood samples were collected in EDTA-containing tubes. Genomic DNA was extracted using standard laboratory procedures.

NGS-based genetic analysis was performed using a panel of genes associated with cardiomyopathy and cardiac structural and functional disorders. The analysis included genes such as TTN, LMNA, MYH7, DSP, BAG3, TNNT2, and other cardiomyopathy-associated genes.

Sequence alignment, variant calling, annotation, and interpretation were performed according to standard bioinformatic procedures. Genetic variants were classified according to the recommendations of the American College of Medical Genetics and Genomics (ACMG) as pathogenic, likely pathogenic, or variants of uncertain significance (VUS) (Richards *et al*., 2015).

2.7. Statistical analysis

This study was a descriptive case series involving three patients, no inferential statistical analysis was performed. Clinical, laboratory, imaging, and genetic findings were presented descriptively for each individual case.

2.8. Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. Written

informed consent was obtained from the parents or legal guardians of the pediatric patients. Ethical approval was obtained from the institutional ethics committee of the participating centers.

3. Case Series

3.1. General clinical characteristics

Three children aged 6–13 years were evaluated with the progressive symptoms of heart failure. All patients demonstrated reduced exercise tolerance, dyspnea, fatigue, growth retardation, and signs of chronic heart failure.

The duration of symptoms ranged from approximately one to three years. Disease onset occurred between 5 and 10 years of age.

A relevant family history of cardiovascular disease was present in all three cases. In one case, the patient's father died suddenly at the age of 29 years. In another case, a brother died at the age of 19 years. In the third case, the patient's father had a history of myocarditis.

None of the cases had a reported history of consanguineous marriage.

3.2. Clinical Case 1

A 13-year-old boy was admitted with dyspnea at rest and during minimal physical activity, marked fatigue, emotional lability, poor appetite, cyanosis of the nasolabial triangle, intermittent cough, and abdominal pain.

The symptoms had been present for approximately three years, with disease onset at the age of 10 years. His medical history included varicella and recurrent acute respiratory viral infections.

Physical examination demonstrated delayed physical development. The family history was notable for the sudden death of the patient's father at the age of 29 years. No consanguinity was reported.

The initial diagnosis was dilated cardiomyopathy complicated by stage IIB chronic heart failure. Concomitant conditions included allergic rhinitis and chronic gastroduodenitis.

The clinical presentation in this patient was notable for the persistence of symptoms over approximately three years before the reported evaluation. Breathlessness at rest and during minimal physical activity, together with fatigue and poor appetite, indicates substantial limitations in daily functioning. The reported cyanosis and delayed physical development provide additional context for understanding the patient's overall clinical condition. The family history is also important: the patient's father died suddenly at 29 years of age. Although this history raises concern about a possible inherited cardiac disorder, the cause of the father's death and any underlying genetic diagnosis would need to be established independently. The coexistence of severe DCM and a relevant family history supported the importance of including genetic findings in the overall assessment of this case.

3.3. Clinical Case 2

A 7-year-old boy presented with dyspnea at rest and during minimal physical activity, fatigue, excessive sweating, poor appetite, cyanosis of the nasolabial triangle, and intermittent cough.

Symptoms had persisted for approximately two years, with disease onset at the age of five years. His medical history included hepatitis A, varicella, and an acute intestinal infection.

Growth retardation was observed during examination. The family history revealed the death of a brother at the age of 19 years, raising suspicion of familial cardiomyopathy. No consanguinity was reported.

The patient was diagnosed with DCM complicated by stage IIB chronic heart failure, grade I respiratory failure, polyserositis, hydropericardium, and bilateral hydrothorax.

Compared with the other cases, this patient's recorded presentation included several additional complications. In addition to breathlessness, fatigue, sweating, poor appetite, and cyanosis, the clinical record documented respiratory failure, polyserositis, hydropericardium, and bilateral hydrothorax. These findings indicate that the clinical assessment involved more than ventricular dysfunction alone and included associated respiratory and serosal abnormalities. The history of symptoms beginning at five years of age and persisting for approximately two years provides a further description of the disease course before evaluation. The death of the patient's brother at 19 years of age is an important element of the family history, although the available information does not establish the cause of death or confirm that the brother had cardiomyopathy. These observations illustrate the need to consider both individual complications and family history when describing pediatric DCM.

3.4. Clinical Case 3

A 6-year-old girl was admitted with dyspnea at rest and during minimal physical activity, fatigue, weight loss, cyanosis of the nasolabial triangle, and intermittent cough.

The duration of symptoms was approximately one year, with disease onset at the age of five years. Her medical history included recurrent acute respiratory viral infections.
Delayed physical development was observed. The patient's father had a history of myocarditis. No consanguineous marriage was reported.
The initial diagnosis was DCM complicated by stage IIB chronic heart failure. Concomitant conditions included liver cirrhosis and refractive asthenopia.
The third patient presented at a younger age than the other two children and had the shortest reported duration of symptoms, approximately one year. Despite this difference in duration, the documented presentation included breathlessness at rest and during minimal activity, fatigue, weight loss, cyanosis, and delayed physical development. Ventricular dysfunction and the associated clinical findings therefore need to be considered in the context of her age and overall health. The reported history of liver cirrhosis is an additional clinical feature that deserves careful documentation, although the available information does not establish its cause or relationship to the cardiomyopathy. Her father's history of myocarditis is relevant to the family history but does not, by itself, establish an inherited cardiac disorder. This case reinforces the importance of documenting associated conditions separately from findings directly attributed to DCM.

4. Clinical and Laboratory Findings
The main clinical characteristics of the three patients are summarized in Table 1**.**

Table 1. Clinical characteristics and medical history of the pediatric patients with familial DCM

Parameter	Case 1	Case 2	Case 3
Age, years	13	7	6
Sex	Male	Male	Female
Duration of symptoms	3 years	2 years	1 year
Age at disease onset	10 years	5 years	5 years
Growth retardation	Present	Present	Present
Family history	Father died at 29 years	Brother died at 19 years	Father had myocarditis
Consanguinity	No	No	No
Protein-energy malnutrition	−2 SD	Reported	Reported
Initial diagnosis	DCM, CHF stage IIB	DCM, CHF stage IIB	DCM, CHF stage IIB
Major complications	—	Respiratory failure, polyserositis, hydropericardium, bilateral hydrothorax	—
Comorbidities	Allergic rhinitis, chronic gastroduodenitis	None reported	Liver cirrhosis, refractive asthenopia

Laboratory investigations demonstrated biochemical abnormalities in all three patients.
NT-proBNP was elevated in all cases, with the highest value observed in Case 1 (6930 pg/mL). Troponin I and CK-MB levels were increased, indicating myocardial injury.
AST/ALT ratios were elevated in all three patients, suggesting hepatic involvement in the setting of chronic heart failure. Lactate levels were reported to be elevated in Cases 1 and 3. CRP levels indicated mild-to-moderate inflammatory activity.
Electrolyte abnormalities included hypocalcemia and hyperkalemia in all patients, while hypernatremia was more pronounced in Cases 2 and 3. Anemia was also observed, with the lowest hemoglobin concentration recorded in Case 3 (77 g/L).
The laboratory results showed differences in the degree of abnormality among the three patients. Case 1 had the highest NT-proBNP concentration (6,930 pg/mL), whereas the values in Cases 2 and 3 were 780 pg/mL and 660 pg/mL, respectively. This variation is notable because all three patients had severely reduced left ventricular ejection fractions. However, the results from this small case series do not

establish a direct relationship between NT-proBNP concentration and the severity or progression of the disease.

Troponin I and CK-MB were also elevated relative to the reference ranges reported in Table 2. These findings add to the description of the biochemical profile accompanying the patients' cardiac abnormalities. The reported electrolyte disturbances, including reduced calcium and increased potassium, were present in all three cases, while the lowest hemoglobin concentration was observed in Case 3. Although these abnormalities are clinically relevant, their causes and relationship to the underlying cardiomyopathy cannot be determined from the available measurements alone. The laboratory findings should therefore be interpreted alongside the clinical presentation and echocardiographic results rather than as independent indicators of disease progression.

Table 2. Laboratory findings in the pediatric patients with familial DCM

Parameter	Case 1	Case 2	Case 3	Reference values
NT-proBNP, pg/mL	6930	780	660	<125
Troponin I, ng/mL	0.08	0.04	0.06	<0.04
CK-MB, U/L	48	36	52	0–25
AST/ALT ratio	1.9	1.8	2.0	<1.0
Lactate*	231	198	277	90–180
CRP, mg/L	9	8	14	<5
Ca^{2+}, mmol/L	2.0	1.8	2.0	2.1–2.6
K^{+}, mmol/L	5.8	5.3	5.9	3.5–5.1

**The unit of lactate measurement should be verified against the original laboratory report before submission.*

5. Instrumental Findings

Electrocardiographic examination revealed persistent rhythm abnormalities. Case 1 demonstrated sinus tachycardia, Case 2 sinus arrhythmia, and Case 3 ventricular extrasystoles.

Holter monitoring findings were consistent with the standard ECG results and did not demonstrate sustained malignant arrhythmias.

Comparative Interpretation of Clinical and Instrumental Findings

Comparison of the three cases revealed a consistently severe degree of left ventricular systolic dysfunction, despite differences in age, symptom duration, and recorded rhythm abnormalities. The ejection fraction was 23% in Case 1 and 22% in both Cases 2 and 3. These closely grouped values indicate that all three children had markedly impaired left ventricular systolic function at the time of assessment.

Left ventricular end-diastolic diameter z-scores were also substantially elevated in all patients. The highest reported value was +6.5 in Case 1, followed by +6.2 in Case 3 and +5.8 in Case 2. These measurements demonstrate pronounced ventricular dilatation relative to the pediatric reference values used in the study. Although Case 1 had the highest reported z-score, the small number of patients does not allow a reliable conclusion that the differences reflect distinct disease subtypes or predict different long-term outcomes.

The electrocardiographic findings were not identical across the cases. Sinus tachycardia was reported in Case 1, sinus arrhythmia in Case 2, and ventricular extrasystoles in Case 3. This variation is relevant because the clinical assessment of DCM includes both ventricular function and the detection of rhythm disturbances. The available results do not establish sustained malignant arrhythmias in these patients, and the recorded findings should not be interpreted as evidence that all three children had the same arrhythmic risk.

Mitral regurgitation graded I–II was reported in each patient. In the context of marked ventricular enlargement, this finding may be compatible with functional mitral regurgitation, although the mechanism should be interpreted in light of the complete echocardiographic assessment. Pericardial effusion was reported only in Case 2, providing another example of clinical variation among children who otherwise shared severe ventricular dysfunction.

Taken together, the findings demonstrate a common pattern of advanced ventricular impairment accompanied by differences in rhythm and associated cardiac abnormalities. The comparison supports the value of documenting individual clinical features alongside shared characteristics rather than

assuming that a familial presentation necessarily produces an identical phenotype in every affected child.

Echocardiography demonstrated severe structural and functional abnormalities in all three patients. LVEF ranged from 22% to 23%, indicating severe systolic dysfunction.
LVEDD z-scores ranged from +5.8 to +6.5, demonstrating pronounced left ventricular dilatation after adjustment for age and body surface area.
Mild-to-moderate mitral regurgitation (Grade I–II) was observed in all three patients and was considered consistent with functional regurgitation secondary to left ventricular enlargement.
Pericardial effusion was observed in Case 2 but was not detected in Cases 1 and 3.

Table 3. Instrumental findings in the pediatric patients with familial DCM

Parameter	Case 1	Case 2	Case 3
ECG finding	Sinus tachycardia	Sinus arrhythmia	Ventricular extrasystoles
Left ventricular dilatation	Present	Present	Present
LVEF, %	23	22	22
LVEDD z-score	+6.5	+5.8	+6.2
Mitral regurgitation	Grade I–II	Grade I–II	Grade I–II
Pericardial effusion	Absent	Present	Absent
Holter monitoring	Sinus tachycardia	Sinus arrhythmia	Ventricular extrasystoles

6. Echocardiographic and Radiological Findings
Representative echocardiographic findings are shown in Figure 1. All three patients demonstrated marked cardiac enlargement and reduced global left ventricular contractility.



Figure 1. Representative imaging findings in pediatric patients with familial dilated cardiomyopathy.

(A) Case 1: severe global left ventricular hypokinesia with marked four-chamber dilatation. (B) Case 2: pronounced biventricular dilatation with severely reduced left ventricular contractility. (C) Case 3: marked four-chamber enlargement with diffuse left ventricular hypokinesia and severely reduced systolic function.
Chest radiography demonstrated cardiomegaly in all three patients, with varying degrees of pulmonary congestion and edema.

7. Genetic Findings
Genetic analysis identified the same heterozygous splice-site variant in the FLNC gene, c.4737+1G>T, in all three patients.
The variant was classified as likely pathogenic according to ACMG-based interpretation. FLNC encodes filamin C, an important cytoskeletal protein involved in sarcomeric organization and mechanotransduction in cardiomyocytes (Song et al., 2022).
Additional rare heterozygous variants classified as VUS were identified in TNNI3K, MYBPC3, and MAP2K1. A rare variant in RBCK1 was additionally detected in Case 3.
These additional variants were classified as VUS, their contribution to disease development or severity cannot be considered established. They may potentially contribute to phenotypic variability, but further functional and segregation studies would be required to determine their clinical significance.

Interpretation of the FLNC Variant and Additional Genetic Findings

The identification of the same heterozygous FLNC c.4737+1G>T splice-site variant in all three children is the principal molecular observation in this case series. FLNC encodes filamin C, a protein involved in the structural organization of cardiomyocytes. Its role in cardiac muscle makes FLNC relevant when investigating inherited cardiomyopathies, including dilated and arrhythmogenic forms of disease.

The position of a variant at a splice junction is relevant to genetic interpretation because changes affecting RNA splicing may alter the processing of a gene transcript. However, the presence of a splice-site variant alone does not establish the precise molecular consequence in an individual patient. Confirmation of a specific effect, such as abnormal transcript processing, requires appropriate supporting evidence. The present report identifies the variant as likely pathogenic according to the study's interpretation, but the available case descriptions do not provide functional evidence demonstrating its effect on FLNC RNA or protein.

The finding of the same variant in three children with severe DCM is consistent with a possible shared genetic contribution to their clinical presentation. Nevertheless, the strength of this interpretation depends on the supporting variant evidence, the clinical context, and any available family segregation data. The relationship between the reported variant and the family histories should therefore be discussed carefully, without assuming that relatives who were not genetically tested carry the same variant.

Additional variants were reported in TNNI3K, MYBPC3, MAP2K1, and RBCK1. These findings broaden the molecular observations in the case series, but all were classified as variants of uncertain significance. A VUS classification means that the available evidence is insufficient to establish whether a variant is disease-causing or benign. Such a finding should not independently be used to confirm a diagnosis or to attribute a particular clinical feature to that variant.

The possible contribution of these additional variants to differences among the patients remains unresolved. Establishing such a contribution would require further evidence, potentially including family segregation analysis, review of population and clinical databases, and functional studies where appropriate. Until additional evidence becomes available, the FLNC finding and the VUS findings should be reported separately, with their different levels of interpretive certainty made clear.

Table 4. Genetic findings identified in the pediatric patients

Gene	Variant	Case 1	Case 2	Case 3	ACMG classification	Clinical relevance
FLNC	c.4737+1G>T, splice-site	Heterozygous	Heterozygous	Heterozygous	Likely pathogenic	Familial DCM; myofibrillar cardiomyopathy
TNNI3K	c.1673T>C (p.Leu558Pro)	VUS	VUS	VUS	VUS	Cardiac conduction disease ± DCM
MYBPC3	c.2029C>T (p.Pro677Ser)	VUS	VUS	VUS	VUS	Sarcomeric cardiomyopathy
MAP2K1	c.895T>C (p.Ser299Pro)	VUS	VUS	VUS	VUS	RAS/MAPK pathway; cardiac involvement
RBCK1	Variant not fully specified	–	–	Heterozygous	VUS	Immune regulation; possible cardiac involvement

8. Discussion

The case series describes three children with early-onset DCM characterized by severe left ventricular

dilatation, markedly reduced systolic function, chronic heart failure, growth retardation, and relevant family histories of cardiovascular disease.

The clinical presentation was severe in all three patients. LVEF ranged from 22% to 23%, while LVEDD z-scores ranged from +5.8 to +6.5. These findings demonstrate substantial ventricular remodeling and advanced systolic dysfunction.

The presence of cardiovascular disease or premature death among close relatives provides an important clinical indication for genetic evaluation. In the present cases, the family histories included premature death and myocarditis in first- and second-degree relatives.

The major molecular finding was the identification of the heterozygous FLNC c.4737+1G>T splice-site variant in all three patients. The variant was classified as likely pathogenic. FLNC encodes filamin C, a cytoskeletal protein that contributes to the structural organization and mechanical stability of cardiomyocytes (Begay *et al*., 2018; Dong *et al*., 2024).

Disruption of FLNC function has been associated with inherited cardiomyopathies, including dilated and arrhythmogenic phenotypes (Ortiz-Genga *et al*., 2016; Begay *et al*., 2016). Congenital DCM has also been reported in association with biallelic FLNC mutations, further illustrating the potential contribution of FLNC-related genetic defects to early-onset disease (Reinstein *et al*., 2016).

The presence of the same likely pathogenic variant in all three patients provides a plausible genetic explanation for the familial DCM phenotype observed in this case series (Dungu *et al*., 2022).

At the same time, the clinical phenotype was not completely uniform. The patients differed in age at presentation, duration of symptoms, rhythm disturbances, extracardiac manifestations, and severity of complications. These differences may reflect the influence of additional genetic, environmental, or clinical factors (Tayal and Cook, 2016).

Several additional rare variants were detected in TNNI3K, MYBPC3, MAP2K1, and RBCK1. All were classified as VUS. TNNI3K has been associated with cardiac conduction abnormalities and cardiomyopathic phenotypes, whereas MYBPC3 is a major sarcomeric gene associated predominantly with inherited cardiomyopathies. MAP2K1 participates in the RAS/MAPK signaling pathway, which has important roles in cellular growth and development. RBCK1 is involved in ubiquitin-mediated signaling and immune regulation.

However, the identification of VUS does not establish a causal relationship with the observed phenotype. Therefore, these variants should be interpreted cautiously. Their potential contribution to phenotypic variability remains a hypothesis requiring further investigation.

Relationship to Previous Research and Clinical Interpretation

The findings of this case series can be considered in the context of published research on the genetic basis of DCM. Previous studies have investigated the contribution of inherited variants to cardiomyopathy and have demonstrated why genetic findings need to be interpreted alongside the patient's clinical characteristics. Pediatric genetic studies are particularly relevant because the presentation of cardiomyopathy during childhood raises questions about age at onset, disease severity, and the potential value of identifying an inherited cause.

The FLNC finding is a central feature of the present cases. Research on FLNC-associated cardiomyopathy has described relationships between variants in this gene and different cardiomyopathic phenotypes. This literature provides a relevant background for considering the shared variant identified in the three children. Nevertheless, the current case series should not be taken as evidence that all FLNC variants produce the same phenotype. The consequences of an individual variant depend on the available genetic evidence, and the clinical presentation may differ between patients.

A further point of interest is the coexistence of a shared FLNC finding with additional variants classified as VUS. The cases illustrate the distinction between identifying genetic variation and determining its clinical significance. The detection of several rare variants does not necessarily mean that each variant contributes to the disease. In particular, the available findings do not establish that the variants in TNNI3K, MYBPC3, MAP2K1, or RBCK1 account for the differences in symptoms or complications observed among the patients.

The clinical data also demonstrate that patients with a similar degree of ventricular systolic dysfunction can have different associated findings. The three children had closely grouped LVEF values, yet their ECG findings and associated clinical complications were not identical. This observation supports detailed reporting of each patient's phenotype. It does not, however, establish a specific genotype–phenotype relationship, because the series includes only three patients and does not provide sufficient evidence to separate genetic effects from other possible influences.

From a clinical perspective, the findings support an integrated approach to the evaluation of children with suspected familial DCM. Family history, examination, cardiac imaging, rhythm assessment, and

molecular testing provide complementary information. Genetic results may help guide subsequent family evaluation when a clinically relevant variant has been identified, but decisions about relatives should be based on appropriate clinical and genetic assessment rather than on assumptions about their carrier status.
The present series therefore contributes a description of severe pediatric DCM associated with a shared FLNC splice-site variant. Its principal value is the combined presentation of the clinical and molecular observations. Larger studies, additional family testing, and appropriate functional investigations would be needed to clarify the significance of the observed variant in these families and to determine whether the additional VUS have any role in the clinical differences between the patients.

The clinical findings also demonstrate the importance of combining genetic information with detailed phenotypic assessment. Genetic testing alone cannot fully predict disease severity, particularly when additional variants are classified as VUS.
The findings of this case series are consistent with current evidence that genetic testing has an important role in the evaluation of children with unexplained or familial cardiomyopathy (van der Meulen et al., 2022). Identification of a likely pathogenic variant may facilitate genetic counseling and targeted evaluation of relatives (Parker and Landstrom, 2021).
From a clinical perspective, the results support the consideration of cascade family screening in families with early-onset DCM and a relevant history of cardiomyopathy or premature cardiac death. At-risk relatives may benefit from clinical surveillance and targeted genetic testing when a clinically relevant familial variant has been identified (Verdonschot *et al*., 2025; Vissing *et al*., 2022).

Clinical Implications
The cases emphasize the importance of considering an inherited cause when a child presents with DCM and a relevant family history. In such circumstances, genetic evaluation may provide additional information for clinical assessment and may help identify relatives who require further evaluation. The results of genetic testing should be interpreted together with the clinical history, cardiac investigations, and the strength of the evidence supporting the reported variant.
Family assessment is particularly important when the history includes premature death or suspected cardiac disease in close relatives. However, a family history suggestive of inherited disease does not establish the genetic status of individual relatives. Where a clinically relevant familial variant has been confirmed, appropriate genetic counseling and targeted evaluation can help guide decisions about testing and surveillance. The specific approach should follow current clinical guidance and the circumstances of each family.
In the present series, the shared FLNC finding provides a reason to consider the potential value of family-based assessment. The available information does not, by itself, establish the carrier status of untested relatives or determine their individual prognosis. These decisions require appropriate clinical evaluation and, where indicated, genetic testing.

This study has several limitations that should be considered when interpreting the findings. First, the case series included only three children. Although all three had severe DCM and the same reported FLNC splice-site variant, the small sample limits the conclusions that can be drawn about the range of clinical presentations associated with this finding. The observations cannot be generalized to all children with DCM or to all individuals carrying FLNC variants.
Second, the retrospective descriptive design restricted the analysis to the clinical information available in the reviewed records. The study was not designed to establish statistical associations between genetic findings and disease severity, nor can it determine whether the observed differences between patients resulted from genetic, environmental, or other clinical factors.
Third, the additional variants identified in TNNI3K, MYBPC3, MAP2K1, and RBCK1 were classified as variants of uncertain significance. Their contribution to the phenotype therefore remains undetermined. Their presence should not be interpreted as proof of an additional genetic cause of disease without further supporting evidence.
Fourth, the available report does not establish the full extent of family segregation analysis or functional validation of the FLNC variant. These forms of evidence, where available and appropriate, could help clarify the relationship between the molecular finding and the observed phenotype. The family histories are clinically relevant, but they cannot independently demonstrate that the reported variant was inherited in a particular pattern.
Finally, the information presented does not establish the long-term clinical course or outcomes of the three patients. Further follow-up would be needed to describe changes in ventricular function, rhythm

findings, heart failure severity, and clinical status over time. Future studies involving larger pediatric cohorts, detailed family assessment, and additional molecular evidence may help clarify the clinical significance of these observations.

Author Contributions
All Authors contributed equally.

Conflict of Interest
The authors declared that no conflict of interest.

9. Conclusion

Three pediatric patients with familial and genetically determined DCM demonstrated severe early-onset heart failure, marked left ventricular dilatation, and severely reduced systolic function.A heterozygous FLNC c.4737+1G>T splice-site variant, classified as likely pathogenic, was identified in all three patients. Additional rare variants in TNNI3K, MYBPC3, MAP2K1, and RBCK1 were classified as VUS and may potentially contribute to phenotypic variability, although their clinical significance remains uncertain.These findings emphasize the importance of comprehensive genetic evaluation in children with early-onset DCM and a relevant family history. Genetic assessment combined with clinical and echocardiographic follow-up may support earlier diagnosis, family counseling, and identification of relatives who may require further evaluation**.** In addition, the findings highlight the importance of continued clinical observation in children diagnosed with familial DCM. Regular assessment of ventricular function, cardiac dimensions, symptoms, and relevant laboratory parameters may help clinicians recognize changes in clinical status and adjust management when necessary. The integration of genetic information with repeated clinical evaluations may also improve understanding of disease progression within affected families. However, the implications of individual genetic variants should be reassessed as new clinical and molecular evidence becomes available. Continued collaboration between clinicians and genetic specialists is therefore important for interpreting genetic results responsibly and supporting appropriate long-term care for affected children and their relatives.

References

1. Aonuma, K., Ando, K., Kusano, K., Asai, T., Inoue, K., Inamura, Y., ... & HINODE Investigators. (2022). Primary results from the Japanese Heart Failure and sudden cardiac death Prevention Trial (HINODE). ESC heart failure, 9(3), 1584-1596.
2. Arbelo, E., Protonotarios, A., Gimeno, J. R., Arbustini, E., Barriales-Villa, R., Basso, C., ... & Kaski, J. P. (2023). 2023 ESC guidelines for the management of cardiomyopathies: developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC). European heart journal, 44(37), 3503-3626.
3. Avery, E. G., Bartolomaeus, H., Maifeld, A., Marko, L., Wiig, H., Wilck, N., ... & Müller, D. N. (2021). The gut microbiome in hypertension: recent advances and future perspectives. Circulation research, 128(7), 934-950.
4. Bagnall, R. D., Weintraub, R. G., Ingles, J., Duflou, J., Yeates, L., Lam, L., ... & Semsarian, C. (2016). A prospective study of sudden cardiac death among children and young adults. New England Journal of Medicine, 374(25), 2441-2452.
5. Begay, R. L., Graw, S. L., Sinagra, G., Asimaki, A., Rowland, T. J., Slavov, D. B., ... & Taylor, M. R. (2018). Filamin C truncation mutations are associated with arrhythmogenic dilated cardiomyopathy and changes in the cell–cell adhesion structures. *JACC: Clinical Electrophysiology*, *4*(4), 504-514.
6. Begay, R. L., Tharp, C. A., Martin, A., Graw, S. L., Sinagra, G., Miani, D., ... & Taylor, M. R. (2016). FLNC gene splice mutations cause dilated cardiomyopathy. *JACC: Basic to Translational Science*, *1*(5), 344-359.
7. Chen, S. N., Mestroni, L., & Taylor, M. R. (2021). Genetics of dilated cardiomyopathy. *Current opinion in cardiology*, *36*(3), 288.
8. Crasto, S., My, I., & Di Pasquale, E. (2020). The broad spectrum of LMNA cardiac diseases: from molecular mechanisms to clinical phenotype. Frontiers in physiology, 11, 761.
9. Diller, G. P., Gatzoulis, M. A., Broberg, C. S., Aboulhosn, J., Brida, M., Schwerzmann, M., ... & Roos-Hesselink, J. (2021). Coronavirus disease 2019 in adults with congenital heart disease: a position paper from the ESC working group of adult congenital heart disease, and the International Society for Adult Congenital Heart Disease. European heart journal, 42(19), 1858-1865.

10.Dong, R., Zhou, X., Zhang, H., Shi, B., Liu, G., & Liu, Y. (2024). Novel FLNC variants in pediatric cardiomyopathy: an insight into disease mechanisms. *Human Genomics*, *18*(1), 118.
11.Dungu, J. N., Langley, S. G., Hardy-Wallace, A., Li, B., Barbagallo, R. M., Field, D., ... & Savage, H. O. (2022). Dilated cardiomyopathy: the role of genetics, highlighted in a family with Filamin C (FLNC) variant. *Heart*, *108*(9), 676-682.
12.Fernlund, E., Kissopoulou, A., Green, H., Karlsson, J. E., Ellegård, R., Årstrand, H. K., ... & Gunnarsson, C. (2020). Hereditary hypertrophic cardiomyopathy in children and young adults—The value of reevaluating and expanding gene panel analyses. Genes, 11(12), 1472.
13.Harrison, S. M., Biesecker, L. G., & Rehm, H. L. (2019). Overview of specifications to the ACMG/AMP variant interpretation guidelines. Current protocols in human genetics, 103(1), e93.
14.Ismail, A., Khreis, D., Assaad, A., & Majdalani, M. N. (2024). Familial dilated cardiomyopathy in a child: a case report. BMC pediatrics, 24(1), 226.
15.Khan, R. S., Pahl, E., Dellefave-Castillo, L., Rychlik, K., Ing, A., Yap, K. L., ... & Webster, G. (2022). Genotype and cardiac outcomes in pediatric dilated cardiomyopathy. Journal of the American Heart Association, 11(1), e022854.
16.Landstrom, A. P., Kim, J. J., Gelb, B. D., Helm, B. M., Kannankeril, P. J., Semsarian, C., ... & Ware, S. M. (2021). Genetic testing for heritable cardiovascular diseases in pediatric patients: a scientific statement from the American Heart Association. *Circulation: Genomic and Precision Medicine*, *14*(5), e000086. of Molecular Sciences, 26(12), 5900.
17.Landstrom, A. P., Kim, J. J., Gelb, B. D., Helm, B. M., Kannankeril, P. J., Semsarian, C., ... & Ware, S. M. (2021). Genetic testing for heritable cardiovascular diseases in pediatric patients: a scientific statement from the American Heart Association. *Circulation: Genomic and Precision Medicine*, *14*(5), e000086.
18.Lee, T. M., Hsu, D. T., Kantor, P., Towbin, J. A., Ware, S. M., Colan, S. D., ... & Lipshultz, S. E. (2017). Pediatric cardiomyopathies. Circulation research, 121(7), 855-873.
19.Malinow, I., Fong, D. C., Miyamoto, M., Badran, S., & Hong, C. C. (2024). Pediatric dilated cardiomyopathy: a review of current clinical approaches and pathogenesis. Frontiers in Pediatrics, 12, 1404942.
20.Marchetti, G. B., Gaudioso, F., Meossi, C., Mura, M., Agostoni, C., Gervasini, C., ... & Milani, D. (2026). Keeping up the beat of Kleefstra syndrome. *Italian Journal of Pediatrics*, *52*(1), 38.
21.McKenna, W. J., & Judge, D. P. (2021). Epidemiology of the inherited cardiomyopathies. Nature Reviews Cardiology, 18(1), 22-36.
22.Muñoz, J. J. S., Muñoz-Esparza, C., Verdú, P. P., Sánchez, J. M., Almagro, F. G., Ruiz, G. E., ... & Alberola, A. G. (2021). Catheter ablation of ventricular arrhythmias in left ventricular noncompaction cardiomyopathy. Heart Rhythm, 18(4), 545-552.
23.Nie, S. F., Yu, M., Xie, T., Yang, F., Wang, H. B., Wang, Z. H., ... & Cheng, X. (2020). Cardiac troponin I is an independent predictor for mortality in hospitalized patients with COVID-19. Circulation, 142(6), 608-610.
24.Ortiz-Genga, M. F., Cuenca, S., Dal Ferro, M., Zorio, E., Salgado-Aranda, R., Climent, V., ... & Monserrat, L. (2016). Truncating FLNC mutations are associated with high-risk dilated and arrhythmogenic cardiomyopathies. *Journal of the American College of Cardiology*, *68*(22), 2440-2451.
25.Pappritz, K., Lin, J., El-Shafeey, M., Fechner, H., Kühl, U., Alogna, A., ... & Van Linthout, S. (2022). Colchicine prevents disease progression in viral myocarditis via modulating the NLRP3 inflammasome in the cardiosplenic axis. ESC Heart Failure, 9(2), 925-941.
26.Parker, L. E., & Landstrom, A. P. (2021). The clinical utility of pediatric cardiomyopathy genetic testing: From diagnosis to a precision medicine-based approach to care. *Progress in pediatric cardiology*, *62*, 101413.
27.Reinstein, E., Gutierrez-Fernandez, A., Tzur, S., Bormans, C., Marcu, S., Tayeb-Fligelman, E., ... & Lopez-Otın, C. (2016). Congenital dilated cardiomyopathy caused by biallelic mutations in Filamin C. *European Journal of Human Genetics*, *24*(12), 1792-1796.
28.Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., ... & Rehm, H. L. (2015). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in medicine*, *17*(5), 405-423.
29.Roest, S., Bunge, J. J., & Manintveld, O. C. (2020). Extracorporeal cardiopulmonary resuscitation in out-of-hospital cardiac arrest in relation to organ donation. European Heart Journal, 41(37), 3587-3587.
30.Sengupta, A., Gauvreau, K., Kohlsaat, K., Colan, S. D., Newburger, J. W., Del Nido, P. J., & Nathan, M. (2022). Intraoperative residual lesion score predicts predischarge major residual lesions and

reinterventions following congenital heart surgery. Journal of the American College of Cardiology, 80(12), 1202-1204.
31.Song, S., Shi, A., Lian, H., Hu, S., & Nie, Y. (2022). Filamin C in cardiomyopathy: from physiological roles to DNA variants. *Heart Failure Reviews*, *27*(4), 1373-1385.
32.Takacs, H., Hategan, L., Csanyi, B., Nagy, V., Borbas, J., Racz, G., ... & Sepp, R. (2024, July). The genetic architecture of dilated cardiomyopathy in Hungary: analysis of 135 patients with a panel of 98 genes. In EUROPEAN JOURNAL OF HEART FAILURE (Vol. 26, pp. 530-530). 111 RIVER ST, HOBOKEN 07030-5774, NJ USA: WILEY.
33.Tayal, U., & Cook, S. A. (2016). Truncating variants in filamin C: the challenges of genotype-phenotype correlations in cardiomyopathies. *Journal of the American College of Cardiology*, *68*(22), 2452-2453.
34.Tayal, U., Newsome, S., Buchan, R., Whiffin, N., Walsh, R., Barton, P. J., ... & Prasad, S. K. (2017). Truncating variants in titin independently predict early arrhythmias in patients with dilated cardiomyopathy. *Journal of the American College of Cardiology*, *69*(19), 2466-2468.
35.van der Meulen, M. H., Herkert, J. C., den Boer, S. L., du Marchie Sarvaas, G. J., Blom, N. A., Ten Harkel, A. D., ... & Dalinghaus, M. (2022). Genetic evaluation of a nation-wide Dutch pediatric DCM cohort: the use of genetic testing in risk stratification. *Circulation: Genomic and Precision Medicine*, *15*(5), e002981.
36.Vasilescu, C., Ojala, T. H., Brilhante, V., Ojanen, S., Hinterding, H. M., Palin, E., ... & Suomalainen, A. (2018). Genetic basis of severe childhood-onset cardiomyopathies. Journal of the American College of Cardiology, 72(19), 2324-2338.
37.Verdonschot, J. A., Hazebroek, M. R., Krapels, I. P., Henkens, M. T., Raafs, A., Wang, P., ... & Brunner, H. G. (2020). Implications of genetic testing in dilated cardiomyopathy. Circulation: Genomic and Precision Medicine, 13(5), 476-487.
38.Verdonschot, J. A., Kaski, J. P., Asselbergs, F. W., Behr, E. R., Charron, P., Dawson, D., ... & Garcia-Pavia, P. (2025). Clinical care of family members of patients with dilated cardiomyopathy: A clinical consensus statement of the Heart Failure Association of the European Society of Cardiology, the European Society of Cardiology Working Group on Myocardial & Pericardial Diseases, and the European Society of Cardiology Council on Cardiovascular Genomics. *European heart journal*, *46*(43), 4569-4582.
39.Verdonschot, J. A., van Spaendonck-Zwarts, K. Y., Hellebrekers, D. M., Asselbergs, F. W., Behr, E. R., Charron, P., ... & Van Tintelen, J. P. (2026). Genetic counselling implementation in dilated cardiomyopathy: A clinical consensus statement of the Heart Failure Association of the ESC, the ESC Working Group on Myocardial and Pericardial Diseases, and the ESC Council on Cardiovascular Genomics. European heart journal, 47(24), 3040-3051.
40.Vissing, C. R., Espersen, K., Mills, H. L., Bartels, E. D., Jurlander, R., Skriver, S. V., ... & Bundgaard, H. (2022). Family screening in dilated cardiomyopathy: prevalence, incidence, and potential for limiting follow-up. *Heart Failure*, *10*(11), 792-803.
41.Ware, J. S., & Cook, S. A. (2018). Role of titin in cardiomyopathy: from DNA variants to patient stratification. Nature Reviews Cardiology, 15(4), 241-252.
42.Ware, S. M., Wilkinson, J. D., Tariq, M., Schubert, J. A., Sridhar, A., Colan, S. D., ... & Pediatric Cardiomyopathy Registry Study Group. (2021). Genetic causes of cardiomyopathy in children: first results from the pediatric cardiomyopathy genes study. *Journal of the American Heart Association*, *10*(9), e017731.
43.Weldy, C. S., & Ashley, E. A. (2021). Towards precision medicine in heart failure. Nature Reviews Cardiology, 18(11), 745-762.
44.Wilsbacher, L. D. (2020). Clinical implications of the genetic architecture of dilated cardiomyopathy. *Current cardiology reports*, *22*(12), 170.
45.Xiao, F., Wei, Q., Wu, B., Liu, X., Mading, A., Yang, L., ... & Wang, H. (2020). Clinical exome sequencing revealed that FLNC variants contribute to the early diagnosis of cardiomyopathies in infant patients. *Translational Pediatrics*, *9*(1), 21.