Neonatal Cardiac Dilation and Dysfunction: Time to Look in the Genes

Meaghan C. Rousset, MD,[1] Sudeep D. Sunthankar, MD, MSc[2]

Cardiomyopathy is a disease of the myocardium that can present with ventricular hypertrophy, dilation, or dysfunction and subsequently result in clinical heart failure. Dilated cardiomyopathy is the most common phenotype; however, it can be difficult to differentiate from myocarditis, particularly in neonates. Important causes of ventricular dysfunction in the pediatric population range from primary cardiomyopathies that affect the structure or function of the myocardium to systemic diseases that lead to secondary myocardial injury. We describe a term newborn who presented with a cardiac murmur and cyanotic spell and subsequently was found to have biventricular dysfunction on echocardiogram. Due to a positive respiratory viral panel for enterovirus, the patient was thought to have viral myocarditis; however, biomarkers revealed no evidence of systemic or myocardial inflammation on laboratory investigation. Furthermore, severe right ventricular dilation was present, which was less consistent with myocarditis. A primary cardiomyopathy was suspected, and genetic testing revealed a likely pathogenic variant of the *ACTC1* gene. This case demonstrates the diagnostic dilemma of determining the etiology in neonatal cardiomyopathy and highlights the utility of genetic testing for diagnostic and prognostic information in such clinical scenarios.

INTRODUCTION

Cardiac murmurs are encountered on the newborn physical examination and can represent a benign finding or, more rarely, significant cardiac disease.[1,2] Red flag symptoms in such cases include family history of congenital heart disease, central cyanosis, respiratory distress, markers of systemic malperfusion, and a failed newborn critical congenital heart disease screen.[1] Timely completion of cardiac evaluation in infants with red flag symptoms is appropriate for early detection of cardiac defects.

Workup in such situations includes an echocardiogram. Isolated ventricular dysfunction can be incidentally detected on an echocardiogram in the newborn and may represent a transitional finding; however, the presence of significant ventricular dysfunction and clinical symptoms may require escalation of care and additional evaluation. The differential diagnosis, in cases of neonatal ventricular dysfunction, is broad and can include infectious, metabolic, and primary cardiac disease. Specifically, neonatal conditions that present with ventricular dysfunction include myocarditis, primary cardiomyopathy, valvular disease, coronary anomalies, and in utero or postnatal arrhythmias.[3–7] Thorough acquisition of family history, clinical assessment, laboratory workup (eg, viral serology, metabolic, and genetic testing), and echocardiographic assessment can assist in working through this differential.[4] Herein, we report a case of a term–gestational age newborn with

[1]*Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee; and* [2]*Thomas P. Graham Jr. Division of Pediatric Cardiology and Center for Pediatric Precision Medicine, Department of Pediatrics, Monroe Carell Jr. Children's Hospital at Vanderbilt and Vanderbilt University Medical Center, Nashville, Tennessee*

Address correspondence to: Meaghan C. Rousset, MD, Department of Pediatrics, 2200 Children's Way, Doctors' Office Tower Suite 2404, Nashville, TN 37232-9119. meaghan.rousset@vumc.org

Dr Rousset drafted the initial manuscript, participated in the concept and design, participated in analysis and interpretation of data, and reviewed and revised the manuscript. Dr Sunthankar obtained consent from the patient's family, conceptualized the case report, participated in interpretation of data, and critically reviewed and revised the manuscript. Both authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST DISCLOSURE: The authors have no conflicts of interest to disclose.

FUNDING: No specific funding or support was secured for this study.

Accepted for Publication Date: March 26, 2025

https://doi.org/10.1542/peds.2024-070005

To cite: Rousset MC and Sunthankar SD. Neonatal Cardiac Dilation and Dysfunction: Time to Look in the Genes. *Pediatrics*. 2025;155(6):e2024070005

murmur, cyanotic spells, and respiratory distress in the newborn nursery with echocardiogram revealing biventricular dysfunction.

CASE PRESENTATION

We present a term newborn, birth weight of 3.317 kg, born at a local hospital with an uncomplicated pregnancy and delivery. Shortly after birth, the patient had cyanotic spells. Respiratory viral panel findings were positive for enterovirus, and echocardiogram showed mildly dilated left ventricle (LV) with mildly depressed wall motion, severely hypertrophied and dilated right ventricle (RV) with moderate to severely depressed RV wall motion, and moderate-to-severe tricuspid regurgitation prompting transfer to a local neonatal intensive care unit. Over the following 5 days, the patient had escalation of respiratory and inotropic support requiring intubation, milrinone, and dobutamine. Biventricular wall motion remained unchanged. Cardiac biomarkers included borderline elevated troponin-I concentration (0.09 ng/mL; normal < 0.03 ng/mL). Given her tenuous clinical status, she was transferred to our facility on day of life (DOL) 6, with a diagnosis of enterovirus myocarditis, for consideration of extracorporeal membrane oxygenation.

Admission cardiac biomarkers were notable for an elevated B-type natriuretic peptide level (1891 pg/mL) and normal troponin level (0.03 ng/mL). Echocardiogram (DOL 6) detected severely depressed biventricular wall motion (LV ejection fraction [5% area-length] = 12%; Figure 1, Supplemental Movie S1), severely dilated and hypertrabeculated RV, moderate right atrial dilation, mild-to-moderate tricuspid regurgitation, systemic RV pressures, an atrial septal defect, and normal coronary artery origins.

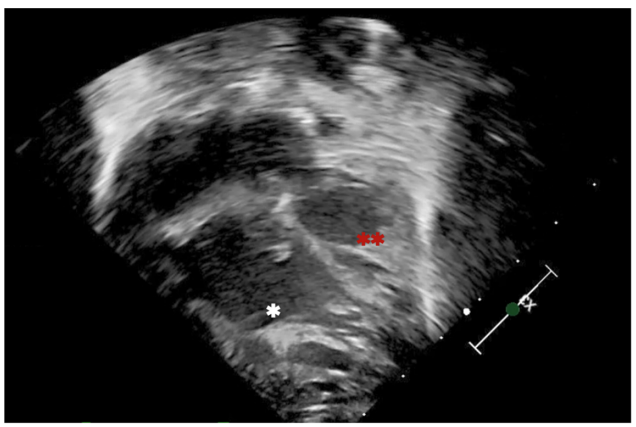

FIGURE 1.
Transthoracic echocardiogram with severe right ventricular dilation (white asterisk), moderate tricuspid regurgitation, normal left ventricular (double red asterisk) size with significant hypertrabeculation, and markedly depressed right and left ventricular wall motion.

Electrocardiogram (ECG) showed sinus rhythm without PR-segment or ST-segment changes. Complete results from admission laboratory and echocardiogram measurements are included in Table 1. Given the abnormal RV morphology and severe biventricular dysfunction in the absence of troponinemia, rapid genome sequencing was performed to investigate primary cardiomyopathies. This resulted on DOL 16 with a de novo heterozygous likely pathogenic variant in the actin alpha cardiac muscle 1 (*ACTC1*) gene c.893A>G (p.Asn298Ser). The patient was given the diagnosis of *ACTC1*-related autosomal dominant dilated cardiomyopathy type 1R.

Despite persistent biventricular dysfunction, end-organ function remained normal. Thus, she was considered for heart transplantation; however, a cardiac catheterization revealed elevated pulmonary vascular resistance (5.9 Wood units × m^2; normal < 3.0 Wood units × m^2) on 100% fraction of inspired oxygen and 40-ppm inhaled nitric oxide. Given the elevated pulmonary vascular resistance on pulmonary vasodilator therapy, we determined the patient was not a transplant candidate. The patient's severe pulmonary hypertension was suspected to be secondary to LV dysfunction given the patient's elevated LV end-diastolic pressure, left atrial pressure, and pulmonary capillary wedge pressure on cardiac catheterization (Supplemental Figure S2). The *ACTC1* gene mutation did not have a reported association with pulmonary hypertension, and there were no additional genes identified on the exome sequencing to explain the severe pulmonary hypertension. Treprostinil was started to treat pulmonary hypertension for reconsideration of transplant; however, the patient developed more-frequent refractory hypoxic events suggestive of pulmonary hypertension crises. Due to the patient's clinical instability, cardiac magnetic resonance imaging for tissue characterization was not performed, although it was discussed. The family elected to convert code status to do-not-resuscitate and transition to comfort care; the patient died on DOL 28.

Family and medical team both agreed to an autopsy to evaluate the myocardium with direct and microscopic evaluation to provide additional information to family given this rare cardiogenetic condition. Autopsy revealed both hypertrophy and dilation of RV; microscopic evaluation revealed changes consistent with hypertrophic cardiomyopathy, and the interventricular septum showed myocyte disarray with endocardial fibrosis. The autopsy results did not further explain the patient's severe pulmonary hypertension other than from LV dysfunction. These histologic findings and the grossly observable findings are reported as congruent with the identified likely pathogenic variant in the *ACTC1* gene. Postmortem genetic counseling with the patient's family was held to discuss the de novo variant in *ACTC1* that was consistent with her clinical

TABLE 1. Summary of Admission Laboratory Results

Laboratory Metric	Patient Value	Reference Range
Maternal infectious laboratory tests		
RPR (syphilis)	Nonreactive	Nonreactive
Rubella AB (IgG), antibody index	1.30	≥1.0 Consistent with immunity
Hepatitis B surface antigen	Nonreactive	Nonreactive
Neisseria gonorrhoeae, NAA	Negative	Negative
Chlamydia trachomatis, RNA	Not detected	Not detected
Patient admission laboratory tests		
Hemoglobin, g/dL	12.4	13.5–22.6
Hematocrit, %	36	41.0–65.0
White blood cells, ×103/μL	9.0	9.4–31.1
Platelet count, ×103/μL	151	140–300
C-reactive protein, mg/L	17.3	0.3–6.1
Sodium, mmol/L	139	133–146
Potassium, mmol/L	3.2	3.7–5.9
Chloride, mmol/L	103	98–113
Bicarbonate, mmol/L	26	5–20
Blood urea nitrogen, mg/dL	10	3–22
Creatinine, mg/dL	0.57	0.42–1.05
Glucose, mg/dL	79	50–80
Calcium, mg/dL	8.8	7.6–10.4
Alkaline phosphatase, U/L	118	90–273
Aspartate aminotransferase, U/L	36	32–162
Alanine aminotransferase, U/L	24	5–33
Creatine phosphokinase, U/L	132	29–168
Thyroxine free, ng/dL	1.32	1.05–3.21
Thyroid stimulating hormone, μg/mL	1.717	0.730–4.770
pH (on ABG)	7.44	7.35–7.45
Pco2 (on ABG), mm Hg	43	35.0–48.0
Po2 (on ABG), mm Hg	59	83–108
Bicarbonate (on ABG), mmol/L	29	21.0–28.0
Lactate (whole blood), mmol/L	2.2	0.5–2.2
Troponin, ng/mL	0.03	<0.03
B-type natriuretic peptide, pg/mL	1891	10–100.0
Metabolic newborn screen[a]	Within normal limits	Normal
Organic acids, urine	Without specific patterns of elevation	–
Patient infectious studies		
Respiratory pathogen panel[b]	Detected, rhinovirus/ enterovirus	Not detected
CMV Ab, IgG	Positive	Negative
CMV Ab, IgM	Negative	Negative
Parvovirus B19 Ab, IgG	Positive	Negative
Parvovirus B19 Ab, IgM	Negative	Negative
EBV DNA, PCR	Not detected	No EBV DNA detected
HIV P24 antigen + 1/2 Ab	Nonreactive	Nonreactive
Hepatitis B surface antigen	Negative	Negative
Hepatitis B core Ab	Negative	Negative
Hepatitis C Ab	Negative	Negative
Patient echocardiogram measurements		BSA = 0.22 m^2 for normative value ranges
RV fractional area change, %	1.0	Normal > 35
LV end-diastolic volume, mL	5.1	5.4–15.0
LV posterior wall, cm	0.29	0.30–0.53
Intraventricular septum, cm	0.20	0.33–0.57
LV internal diastolic dimension, cm	1.1	1.7–2.4
LV internal systolic dimension, cm	0.86	1.0–1.6

(Continued on next column)

TABLE 1. Summary of Admission Laboratory Results (Continued)

Abbreviations: Ab, antibody; ABG, arterial blood gas; BSA, body surface area; CMV, cytomegalovirus; EBV, Epstein-Barr virus; IgG, immunoglobulin G; IgM, immunoglobulin M; LV, left ventricle; NAA, nucleic acid amplification; RV, right ventricle.

[a] Screening includes congenital hypothyroidism, galactosemia, hemoglobinopathies, biotinidase deficiency, congenital adrenal hyperplasia, amino acid profile, fatty acid profile, organic acid profile, cystic fibrosis, severe combined immunodeficiency, lysosomal disorders, X-linked adrenoleukodystrophy, and spinal muscular atrophy.

[b] Panel includes SARS-COV-2, influenza A H1, influenza A H3, influenza A 2009 H1N1, influenza B, respiratory syncytial virus (A/B), parainfluenza virus (1–4), metapneumovirus, adenovirus, rhinovirus/enterovirus, coronavirus (HKU1, NL63, 229E, OC43), *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Bordetella pertussis*, and *Bordetella parapertussis*.

phenotype and autopsy findings of a mixed hypertrophic and dilated cardiomyopathy.

DISCUSSION

Ventricular dysfunction in the neonate can pose a diagnostic challenge. In this case, the presence of respiratory distress and cyanotic episode prompted an echocardiogram, which revealed biventricular dysfunction. The presence of a positive viral panel raised suspicion for viral myocarditis; however, the right-chamber dilation and normal troponin level were inconsistent with this diagnosis. Valvular and coronary abnormalities were ruled out by echocardiogram. Cardiac dysrhythmias were not detected on resting ECG or telemetry monitoring, making tachycardia-induced cardiomyopathy unlikely.[8]

Glycogen storage disease, in particular Pompe disease, was considered, but the pathognomonic ECG (short PR interval, large LV voltages) and echocardiogram findings were not seen.[9] Inborn errors of metabolism, including fatty acid oxidation disorders and organic acidurias, were considered less likely because the patient did not have acidosis

on blood work, urine organic acids did not have specific patterns of elevation, and the newborn metabolic screen results were negative.

Enterovirus is a known cause of neonatal myocarditis and can present with cardiogenic shock in the neonate.[6] Although our patient did present with biventricular dysfunction, there was no end organ dysfunction. Myocarditis classically presents with LV enlargement and LV systolic dysfunction on echocardiogram.[10] This was in contrast to our patient's presentation of a severely dilated RV and low-normal size of the LV, which contributed to our suspicion of a different etiology. In addition, the mild elevation of her troponin and inflammatory marker levels was less consistent with myocarditis.[10,11] Given the abnormal appearance to the RV myocardium, RV dilation, and biventricular dysfunction, we focused our workup on a primary cardiomyopathy.

Genetic testing in children with idiopathic cardiomyopathy can provide a definitive molecular diagnosis in a large proportion of these children, so genome sequencing was pursued to expeditiously identify a genetic cardiomyopathy and provide prognostic information for clinical management. The diagnostic yield of genetic testing in pediatric cardiomyopathy does not vary greatly between subtypes of cardiomyopathy; however, the highest yield is typically seen in restrictive cardiomyopathy and the lowest in dilated cardiomyopathy.[12,13] One study examining the diagnostic yield in different categories of pediatric cardiac disease found significantly higher diagnostic rates in patients with isolated cardiomyopathy (approximately 45.5%) compared with isolated congenital heart disease (15.7%).[14] There is significant practice variation in ordering genetic testing for children presenting with idiopathic cardiomyopathy[15]; however, clinical practice guidelines state genetic evaluation of cardiomyopathy is indicated for these cases.[16]

Importantly, a genetic variant underlies a diagnosis of dilated cardiomyopathy in approximately 40% of patients.[17–19] Ultimately, results of the genome sequencing for our patient revealed a de novo, likely pathogenic variant of the *ACTC1* gene with the nucleotide substitution c.893A>G (p.Asn298Ser). The *ACTC1* gene encodes cardiac alpha-actin, which involves formation of the thin contractile filament, allowing for connection of the myocellular Z-disc with the thick filament protein myosin. This gene is important to the functional integrity of cardiomyocytes.[20] The patient was given the diagnosis of *ACTC1*-related autosomal dominant dilated cardiomyopathy type 1R. Although this variant of the *ACTC1* gene has not been previously described in the adult or pediatric population, the *ACTC1* mutation (Gly247Arg) has been identified as a mutation associated with heart failure in the fifth decade of life.[20]

Supportive of this clinical presentation and associated pathogenic variant is the recent literature describing similar cardiac alpha-actin mutations resulting in sarcomere disarray and enhanced apoptotic cardiomyocyte cell death that results in the impairment of cardiomyocyte contractility.[20,21] The significance of this gene has been documented in neonatal mouse models, wherein loss of function of *ACTC1* results in embryonic or perinatal lethality due to cardiac dysfunction.[22] In addition to cardiomyopathy, *ACTC1* mutations are also associated with atrial septal defect and abnormal ventricular morphology, both of which were present in this patient.[21,23] This has been reported as LV noncompaction; however, the abnormal appearance of the RV, in this case, suggests that right ventricular morphology may also be affected.[23]

Our case demonstrated the utility of genome sequencing when primary neonatal cardiomyopathy is suspected. We highlight the importance of early genetic testing when the patient presentation and cardiac findings do not fit with more common diagnoses. Early genetic evaluation may offer the ability to prognosticate disease and expedite appropriate treatment interventions.

CONCLUSION

Differentiating neonatal cardiomyopathy from myocarditis can be a diagnostic challenge faced by pediatric providers in various settings. Providers should have heightened suspicion toward primary cardiomyopathy when there is biventricular dysfunction and normal troponin levels. Neonates with symptomatic cardiomyopathy often have a poor prognosis,[3,11] thus identifying the etiology of cardiomyopathy is essential for counseling families and directing care. Herein, we presented a case of neonatal dilated cardiomyopathy with an associated novel *ACTC1* gene mutation. With advancements in genome sequencing, such testing may be more readily accessible and applicable in such challenging clinical cases.

ABBREVIATIONS

ACTC1: actin alpha cardiac muscle 1
DOL: day of life
ECG: electrocardiogram
LV: left ventricle
RV: right ventricle

REFERENCES

1. Ford B, Lara S, Park J. Heart murmurs in children: evaluation and management. *Am Fam Physician.* 2022;105(3):250–261. PubMed
2. Yoon SA, Hong WH, Cho HJ. Congenital heart disease diagnosed with echocardiogram in newborns with asymptomatic cardiac murmurs: a systematic review. *BMC Pediatr.* 2020;20(1):322. PubMed doi: 10.1186/s12887-020-02212-8
3. Cox GF, Sleeper LA, Lowe AM, et al. Factors associated with establishing a causal diagnosis for children with cardiomyopathy.

Pediatrics. 2006;118(4):1519–1531. PubMed doi: 10.1542/peds.2006-0163

4. Lee TM, Hsu DT, Kantor P, et al. Pediatric cardiomyopathies. *Circ Res*. 2017;121(7):855–873. PubMed doi: 10.1161/CIRCRESAHA.116.309386
5. Maron BJ, Towbin JA, Thiene G, et al; American Heart Association; Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; Council on Epidemiology and Prevention. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation*. 2006;113(14):1807–1816. PubMed doi: 10.1161/CIRCULATIONAHA.106.174287
6. Singanayagam A, Moore C, Froude S, et al. Increased reports of severe myocarditis associated with enterovirus infection in neonates, United Kingdom, 27 June 2022 to 26 April 2023. *Euro Surveill*. 2023;28(39):2300313. PubMed doi: 10.2807/1560-7917.ES.2023.28.39.2300313
7. Soares P, Rocha G, Pissarra S, et al. Neonatal dilated cardiomyopathy. *Rev Port Cardiol*. 2017;36(3):201–214. PubMed doi: 10.1016/j.repc.2016.10.007
8. Gupta S, Figueredo VM. Tachycardia mediated cardiomyopathy: pathophysiology, mechanisms, clinical features and management. *Int J Cardiol*. 2014;172(1):40–46. PubMed doi: 10.1016/j.ijcard.2013.12.180
9. Menahem S, Sehgal A. Left ventricular dysfunction in the newborn. *Transl Pediatr*. 2023;12(5):794–799. PubMed doi: 10.21037/tp-22-666
10. Law YM, Lal AK, Chen S, et al; American Heart Association Pediatric Heart Failure and Transplantation Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young and Stroke Council. Diagnosis and management of myocarditis in children: a scientific statement from the American Heart Association. *Circulation*. 2021;144(6):e123–e135. PubMed doi: 10.1161/CIR.0000000000001001
11. Badertscher A, Bauersfeld U, Arbenz U, Baumgartner MR, Schinzel A, Balmer C. Cardiomyopathy in newborns and infants: a broad spectrum of aetiologies and poor prognosis. *Acta Paediatr*. 2008;97(11):1523–1528. PubMed doi: 10.1111/j.1651-2227.2008.00957.x
12. Bagnall RD, Singer ES, Wacker J, et al. Genetic basis of childhood cardiomyopathy. *Circ Genom Precis Med*. 2022;15(6):e003686. PubMed doi: 10.1161/CIRCGEN.121.003686
13. Keisling J, Bedoukian E, Burstein DS, et al. Diagnostic yield of exome sequencing in pediatric cardiomyopathy. *J Pediatr*. 2024;265:113808. PubMed doi: 10.1016/j.jpeds.2023.113808
14. Slavotinek AM, Thompson ML, Martin LJ, Gelb BD. Diagnostic yield after next-generation sequencing in pediatric cardiovascular disease. *HGG Adv*. 2024;5(3):100286. PubMed doi: 10.1016/j.xhgg.2024.100286
15. Ware SM, Wilkinson JD, Tariq M, et al; Pediatric Cardiomyopathy Registry Study Group. Genetic causes of cardiomyopathy in children: first results from the Pediatric Cardiomyopathy Genes Study. *J Am Heart Assoc*. 2021;10(9):e017731. PubMed doi: 10.1161/JAHA.120.017731
16. Hershberger RE, Givertz MM, Ho CY, et al; ACMG Professional Practice and Guidelines Committee. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2018;20(9):899–909. PubMed doi: 10.1038/s41436-018-0039-z
17. Manca P, Nuzzi V, Cannatà A, et al. The right ventricular involvement in dilated cardiomyopathy: prevalence and prognostic implications of the often-neglected child. *Heart Fail Rev*. 2022;27(5):1795–1805. PubMed doi: 10.1007/s10741-022-10229-7
18. Pugh TJ, Kelly MA, Gowrisankar S, et al. The landscape of genetic variation in dilated cardiomyopathy as surveyed by clinical DNA sequencing. *Genet Med*. 2014;16(8):601–608. PubMed doi: 10.1038/gim.2013.204
19. Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. *Circulation*. 1996;93(5):841–842. PubMed doi: 10.1161/01.CIR.93.5.841
20. Frank D, Yusuf Rangrez A, Friedrich C, et al. Cardiac α-Actin (ACTC1) gene mutation causes atrial-septal defects associated with late-onset dilated cardiomyopathy. *Circ Genom Precis Med*. 2019;12(8):e002491. PubMed doi: 10.1161/CIRCGEN.119.002491
21. Rangrez AY, Kilian L, Stiebeling K, et al. Data on the role of cardiac α-actin (ACTC1) gene mutations on SRF-signaling. *Data Brief*. 2020;28:105071. PubMed doi: 10.1016/j.dib.2019.105071
22. Rangrez AY, Kilian L, Stiebeling K, et al. A cardiac α-actin (ACTC1) p.Gly247Asp mutation inhibits SRF-signaling in vitro in neonatal rat cardiomyocytes. *Biochem Biophys Res Commun*. 2019;518(3):500–505. PubMed doi: 10.1016/j.bbrc.2019.08.081
23. Monserrat L, Hermida-Prieto M, Fernandez X, et al. Mutation in the alpha-cardiac actin gene associated with apical hypertrophic cardiomyopathy, left ventricular non-compaction, and septal defects. *Eur Heart J*. 2007;28(16):1953–1961. PubMed doi: 10.1093/eurheartj/ehm239