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CASE REPORT
Inherited cardiac conditions/cardiomyopathies

Case report: severe hypertrophic cardiomyopathy in a female neonate caused by *de novo* variant in *NDUFB11*

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Background Hypertrophic cardiomyopathy in the neonate has a diverse genetic background, and non-sarcomeric variants may not be identified on commercial genetic testing panels. NDUFB11 is an X-linked mitochondrial Complex I protein and is known to cause histiocytoid cardiomyopathy but has not been described in female infants with hypertrophic cardiomyopathy. We present this first reported case of obstructive hypertrophic cardiomyopathy in a female neonate secondary to a pathogenic variant in NDUFB11.

Case summary A term female neonate presented following a prenatal diagnosis of biventricular hypertrophy and growth restriction. She developed lactic acidosis after birth and whole-genome sequencing identified a *de novo* variant in the mitochondrial Complex I gene, *NDUFB11* (c.391G>A, p.Glu131Lys). There was progression of left ventricular hypertrophy and obstruction, with rapid development of heart failure symptoms. She was unresponsive to beta-blocker medical therapy and was not suitable for advanced mechanical support. There was subsequent clinical deterioration resulting in death by 3 months of age.

Discussion Hemizygous variants in NDUFB11 have been associated with hypertrophic cardiomyopathy in male infants previously, and skewed X-linked inactivation likely resulted in the presentation described here in a female infant. This variant was not identifiable by commercial cardiomyopathy panels. We highlight the importance of rapid whole-genome sequencing in cases of infantile hypertrophic cardiomyopathy and the importance of genetic diagnosis in guiding prognosis and care for these individuals.

Keywords Case report • Hypertrophic cardiomyopathy • Neonatal • Mitochondrial • Whole genome

ESC curriculum 6.5 Cardiomyopathy • 6.1 Symptoms and signs of heart failure • 2.2 Echocardiography

Learning points

- Variants in *NDUFB11* can cause a progressive and severe cardiac phenotype in both male and female infants.
- Rapid whole-genome testing is critical for diagnosis and management of infants with cardiomyopathy.

Introduction

Mitochondrial diseases impact ~1 in every 5000–10 000 births. These manifest in diverse clinical forms and may present with isolated or multiple organ system dysfunction.[1] Cardiomyopathy is frequently observed and leads to higher mortality rates.[1]

Mitochondrial protein Complex I localizes to the inner mitochondrial membrane and contains 14 highly conserved core subunits and 31

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accessory subunits.[2] The assembly functions in the electron transport chain, facilitating oxidative phosphorylation through three modules: a membrane arm (proton pumping 'P' module), a peripheral arm comprising a NADH binding 'N' module, and a ubiquinone-binding 'Q' module[3,4] (*Figure 1*). NADH: ubiquinone oxidoreductase subunit B11 (NDUFB11) is a nuclear-encoded (X chromosome) supernumerary protein of the 'P' module of Complex I.[5–7]

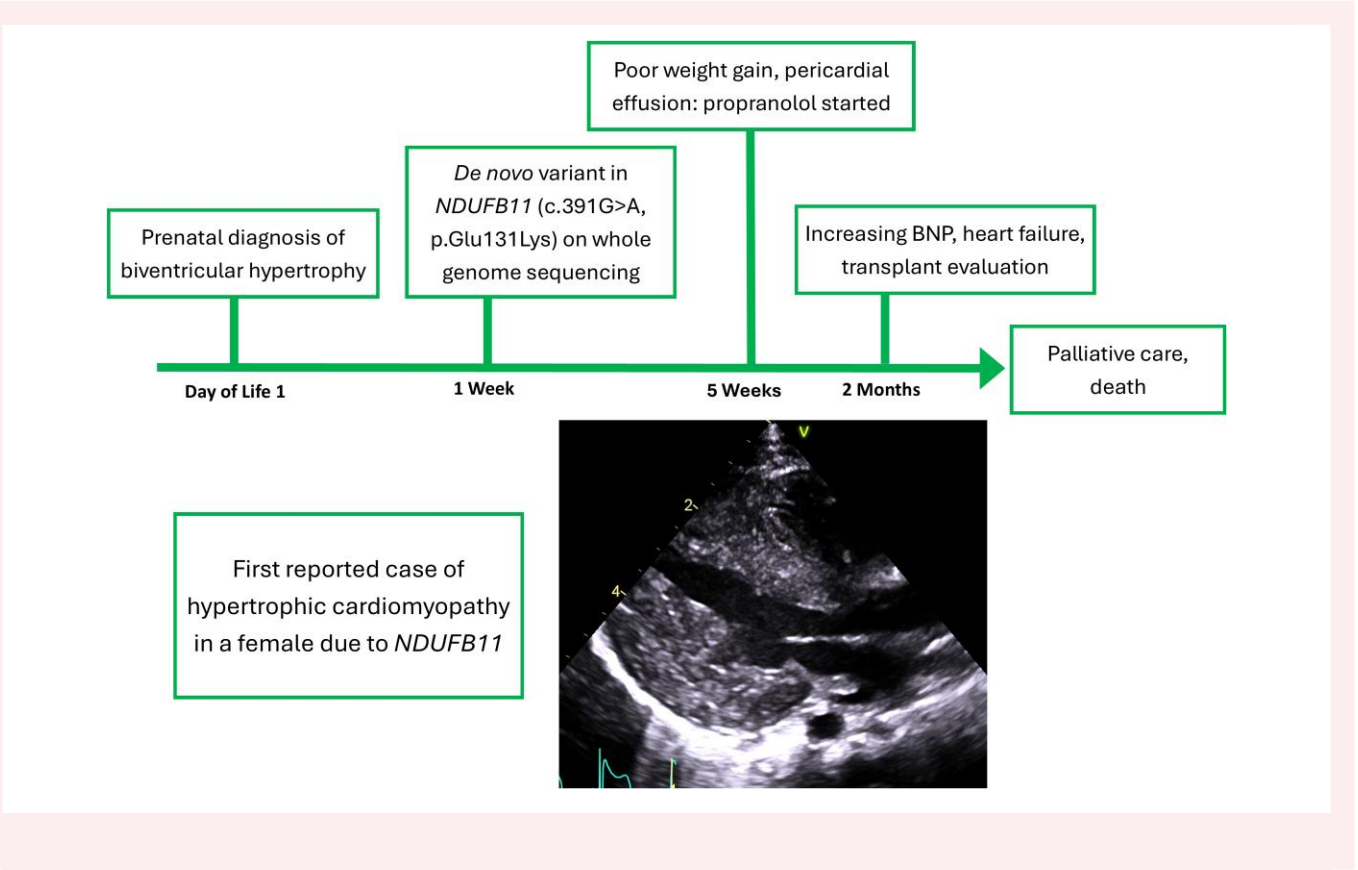
Mutations in *NDUFB11* are typically associated with two distinct conditions: microphthalmia with linear skin defects and histiocytoid cardiomyopathy.[8] Truncating mutations in *NDUFB11* have been associated with hypertrophic cardiomyopathy (HCM) and non-compaction cardiomyopathy in males.[5] These variants are not included in commercially available genetic cardiomyopathy panels. Female carriers are typically asymptomatic, but highly skewed X inactivation may predispose to more severe phenotypes.[9] Here, we present the first reported case of a female neonate with HCM secondary to *de novo* variant in *NDUFB11*.

Summary figure

Timeline of events for the patient from prenatal diagnosis to death.

Case presentation

A female infant was born at full term following prenatal diagnosis of biventricular hypertrophy (*Figure 2*). There was normal maternal glucose tolerance testing and no family history of cardiomyopathy or sudden death. The parents were unrelated, of mixed European descent, and this was the first child for each of them. Physical examination following birth was unremarkable, without syndromic or abnormal features. Postnatal echocardiography confirmed severe non-obstructive left ventricular hypertrophy, and electrocardiogram was notable for ventricular pre-excitation and massive voltages, further raising suspicion for metabolic aetiology (*Figure 3*). Metabolic evaluation was completed with unremarkable amino acid and acyl carnitine profiles. In the absence of systemic hypoperfusion, there was elevated serum lactate (8.1 mmol/L, normal 1.0–3.5 mmol/L) and markedly elevated lactate to pyruvate (0.12 mmol/L, normal 0.03–0.10 mmol/L) ratio (67.5), with ratio above 20 consistent with mitochondrial respiratory chain defect.[10,11] Cardiovascular genetics service consulted and requested rapid whole-exome sequencing of proband and parents, identifying a *de novo* variant in the mitochondrial Complex I gene *NDUFB11* (c.391G>A, p.Glu131Lys). Given the *de novo* variant, further cardiac screening for parents or their children in the future was not recommended.



After multidisciplinary team review of the condition and expected clinical course, parents were counselled regarding the poor prognosis of this condition as well as the likelihood of requiring a heart transplant. She was discharged clinically well and feeding on her own. No arrhythmias were noted on in-hospital or ambulatory rhythm monitoring. At 2 months of age, she developed left ventricular mid-cavitary obstruction and poor weight gain with increasing natriuretic peptide levels (*Figure 4*). Heart failure symptoms progressed rapidly and were unresponsive to beta-blocker therapy, and she developed a large pericardial effusion. Due to her small left atrial size, she was not a candidate for durable ventricular assist device support as a bridge to a heart transplant. Through shared decision-making with her family, she was transitioned to palliative care, and she died by 3 months of age.

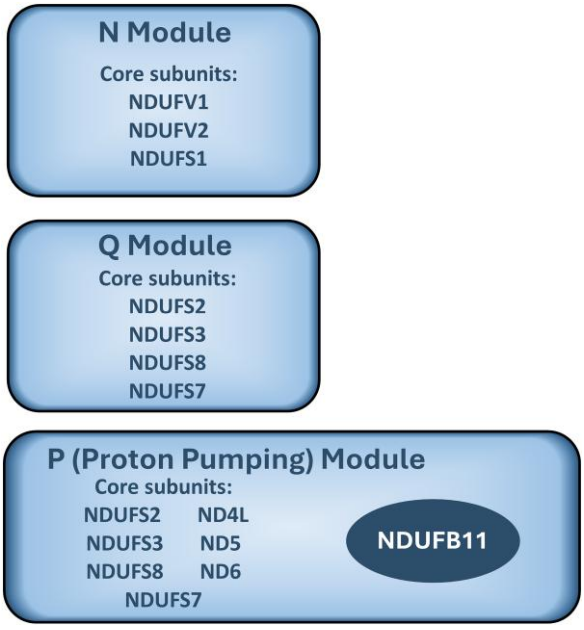


Figure 1 Mammalian Complex 1 core subunits and NDUFB11 supernumerary protein in the P module.

Discussion

In adolescents and adults, sarcomeric gene mutations are responsible for the majority of genotype-positive HCM, but in infants under 1 year of age, left ventricular hypertrophy secondary to mitochondrial, metabolic and syndromic conditions (RASopathy) is common.[12] These phenocopies are typically diagnosed as HCM but carry unique features and prognoses, making genetic diagnosis particularly important.

The protein complexes of the mitochondria are encoded by both the mitochondrial and nuclear genomes. Mutations in the X chromosome-encoded mitochondrial Complex I pore-module protein NDUFB11 have been reported in male infants but are rarely reported in females.[13,14] We provide the first report of HCM in a female secondary to *de novo* mutation in *NDUFB11*. The condition is distinct from the histiocytoid cardiomyopathy reported in this gene, absent cardiac dysfunction and arrhythmias. Variants in genes known to cause disease in the hemizygous state may behave as dominant in cases of highly skewed X inactivation and should be considered as part of diligent genetic evaluation. Genomic filtering algorithms and interpretations should be cautious in considering X-linked recessive variants as non-causative when identified in females with a suggestive phenotype. In cases of less penetrant phenotypes, there may be a role for X chromosome inactivation studies in predicting the severity and need for cardiac transplantation.

The case illustrates the importance for broad testing to evaluate genetic and metabolic causes of neonatal HCM. From a patient perspective, rapid identification of the causative variant allowed for appropriate counselling and support for the family, preparing them for the expected prognosis, and allowing for fully informed decision-making. The current European Society of Cardiology consensus statement recommends genetic testing for probands with HCM for strong evidence of HCM genes but does not provide guidance on the need for exome testing in infants.[15] Genes relating to mitochondrial and metabolic function may be absent from commercial gene panels, including *NDUFB11*. We highlight the importance of rapid diagnosis, through metabolic and whole-exome testing, as critical to understanding disease pathogenesis particularly in infantile cardiomyopathy. As gene replacement and editing strategies evolve, the identification of causative genetic

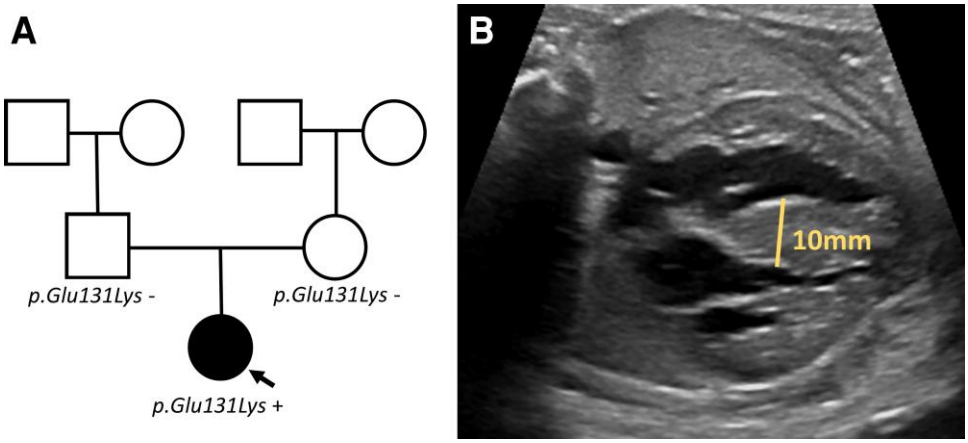


Figure 2 (*A*) Pedigree with *de novo* variant in NDUFB11 p.Glu131Lys in the proband (arrow). (*B*) Routine obstetric ultrasound in late third trimester demonstrated severe myocardial hypertrophy of the interventricular septum (10 mm).

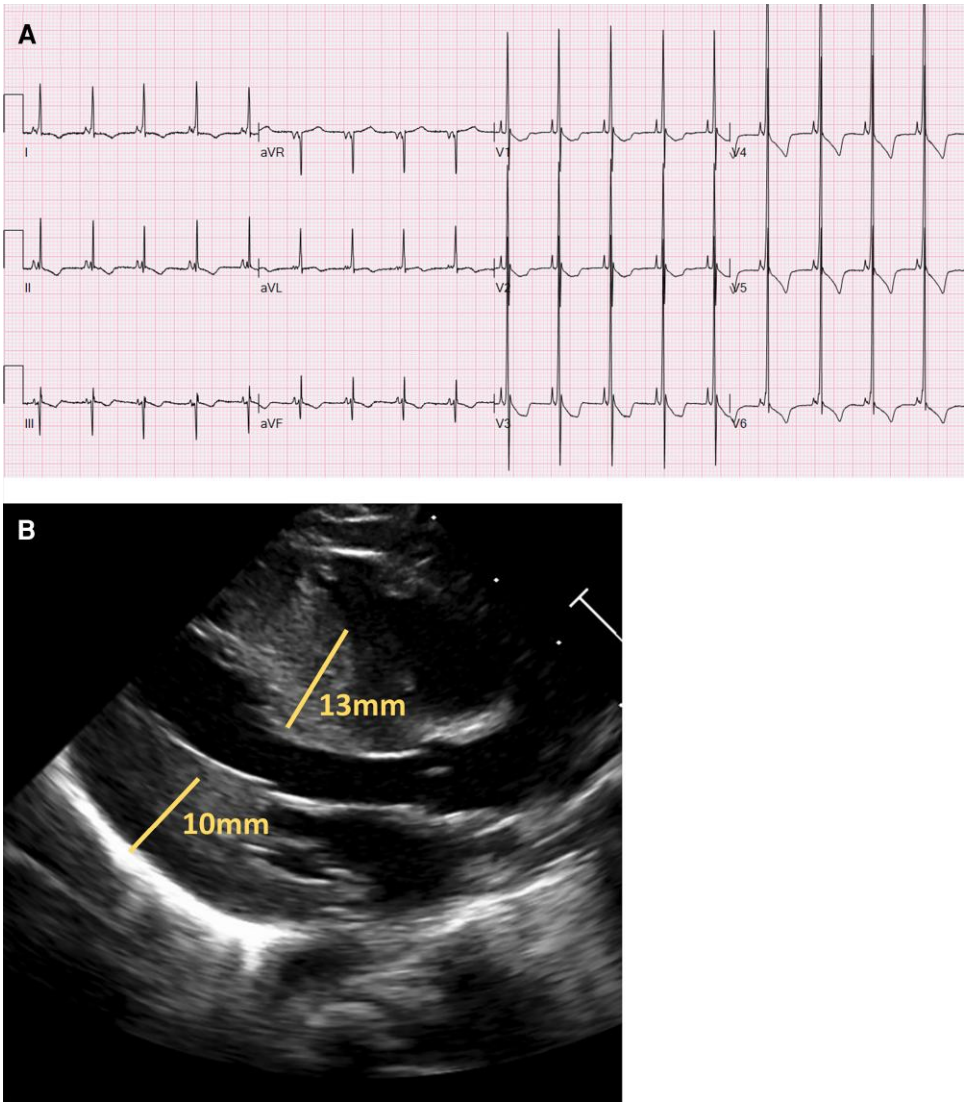


Figure 3 Postnatal evaluation. (*A*) Electrocardiogram with ventricular pre-excitation and massive QRS complex voltages. (*B*) Severe left ventricular hypertrophy on postnatal echocardiography of 13 mm.

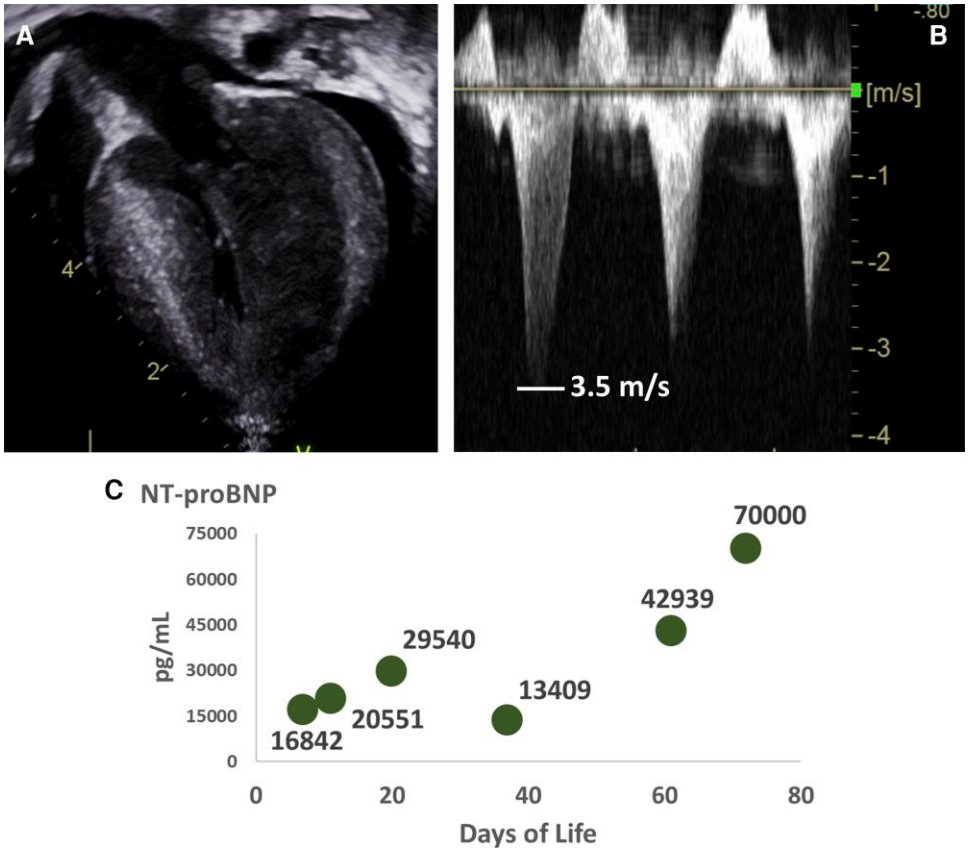


Figure 4 (*A*) Echocardiogram at 2 months old with severe left ventricular hypertrophy and small pericardial effusion. (*B*) Dynamic left-ventricular outflow tract obstruction with peak velocity 3.5 m/s. (*C*) Progressive increase in NT pro-B-natriuretic peptide over the first three months of life (upper limit of normal 125 pg/mL). NT-proBNP, NT pro-B-natriuretic peptide.

variation will be even more crucial for the development of individualized treatment strategies.

Conclusion

We identify the first case of HCM in a female infant secondary to *de novo* mutation in *NDUFB11*. We highlight the need to consider skewed X inactivation and broad genetic testing in neonatal onset cardiomyopathy. Rapid genetic diagnosis is critical for understanding management, prognosis, and developing curative strategies.

Lead author biography

Dr Jeffrey Bennett is a paediatric cardiologist with specialist training in inherited cardiovascular disease. He is interested in genotype–phenotype correlations and genetic testing for congenital and inherited cardiac disease. He is currently director of the Cardiovascular Genetics programme at Cleveland Clinic Children's Hospital.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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