Cardiology in the Young

cambridge.org/cty

Biventricular non-compaction cardiomyopathy and tricuspid hypoplasia in a novel *non-POU domain-containing octamer-binding* gene variant

Sanam Safi[1,2], Stephen P. Sanders[1,3], Melissa Zhao[4] and Chrystalle Katte Carreon[1,5]

[1]Cardiac Registry, Departments of Cardiology, Pathology, and Cardiac Surgery, Boston Children's Hospital, Boston, MA, USA; [2]Department of Cardiology, Gentofte University Hospital, Copenhagen, Denmark; [3]Department of Pediatrics, Harvard Medical School, Boston, MA, USA; [4]Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA and [5]Department of Pathology, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA

Brief Report

Cite this article: Safi S, Sanders SP, Zhao M, and Carreon CK (2022) Biventricular non-compaction cardiomyopathy and tricuspid hypoplasia in a novel *non-POU domain-containing octamer-binding* gene variant. *Cardiology in the Young* **32**: 1333–1337. doi: 10.1017/S1047951121004923

Received: 22 August 2021
Revised: 12 November 2021
Accepted: 15 November 2021
First published online: 12 January 2022

Keywords:
Non-compaction cardiomyopathy; biventricular non-compaction; tricuspid hypoplasia; *non-POU domain-containing octamer-binding gene*; *non-POU domain-containing octamer-binding gene* variant; CHD; *NONO* cardiomyopathy

Author for correspondence:
S. Safi, Cardiac Registry, Departments of Cardiology, Pathology, and Cardiac Surgery, Boston Children's Hospital, Boston, MA, USA.
Tel: +4538673331.
E-mails: sanam.safi@childrens.harvard.edu, sanam.safi@ctu.dk

Abstract

A maternally inherited novel pathogenic *non-POU domain-containing octamer-binding* gene variant c.767G>T, p.R256I [NM_001145408], manifested in a male infant as dilated cardiomyopathy with severe left ventricular dysfunction and dilation, biventricular non-compaction, tricuspid hypoplasia, and hydrocephaly. To the best of our knowledge, no previous *non-POU domain-containing octamer-binding gene* variants with biventricular non-compaction have been associated with tricuspid valve hypoplasia. Hence, this case introduces a new pathogenic variant observed in the *non-POU domain-containing octamer-binding gene* and adds to the range of cardiac phenotypes identified in *non-POU domain-containing octamer-binding gene* variants.

Case report

The patient was a 3-month-old previously healthy boy, born at full-term to healthy, non-consanguineous parents with one older, healthy sibling. He presented at 1 month of age to an outside hospital emergency department after an episode of respiratory distress and cyanosis. A few days prior he had nasal congestion and was noted to have poor weight gain. At the emergency department, he was intubated and subsequently suffered a bradycardic arrest with return of cardiac activity after 2 minutes of compressions and administration of epinephrine and atropine. A chest X-ray revealed cardiomegaly. Electrocardiogram showed normal rhythm with first-degree atrioventricular block and right ventricular hypertrophy. An echocardiogram demonstrated left ventricular dilation and severe dysfunction with possible left ventricular non-compaction, as well as mitral, tricuspid, and aortic regurgitation. He was transferred to our ICU. An echocardiogram demonstrated a severely dilated left ventricle with increased apical and free wall trabeculations and severe systolic dysfunction, right ventricle dysfunction, patent foramen ovale with low-velocity bidirectional flow, bi-atrial enlargement with moderate to severe tricuspid regurgitation, and mild mitral and pulmonary regurgitation (Fig 1A). Whole exome sequencing (performed by GeneDx using Illumina NGS platform) revealed that the patient was hemizygous for a novel and likely pathogenic gene variant in the *non-POU domain-containing octamer-binding gene* c.767G>T, p.R256I [NM_001145408], not previously reported. Both parents underwent whole exome sequencing (GeneDx), and it was determined that the variant was inherited from the patient's mother, who was mosaic for the p.R256I variant in the *non-POU domain-containing octamer-binding gene* with an alternate allele fraction of 12.9%. The variant was considered as likely pathogenic by GeneDx variant classification analysis, which included a Protein Variation Effect Analyzer score of −7.12, representing a deleterious effect. Mitochondrial sequencing was negative. Despite maximal medical management, he continued to deteriorate with severe left ventricular dysfunction, renal failure, worsening hydrocephalus with subclinical seizures, and subsequently expired.

At autopsy, dysmorphic craniofacial features including widened head and inter-canthal distance were noted. The heart was enlarged (85 g, expected for age: 24.7–30.1 g) with biventricular non-compaction (hypertrabeculation) with marked endocardial fibroelastosis (Fig 1B and D), both of which were more severe in the left ventricle. The atria were enlarged with patent foramen ovale and abnormal superior attachment of the septum primum. The tricuspid valve was hypoplastic with an annulus diameter appropriate for age (1.4 cm expected 1.4 +/− 0.5 cm) but with a distally narrower leaflet orifice and shorter chordae than usual (Fig 1D). The right ventricular

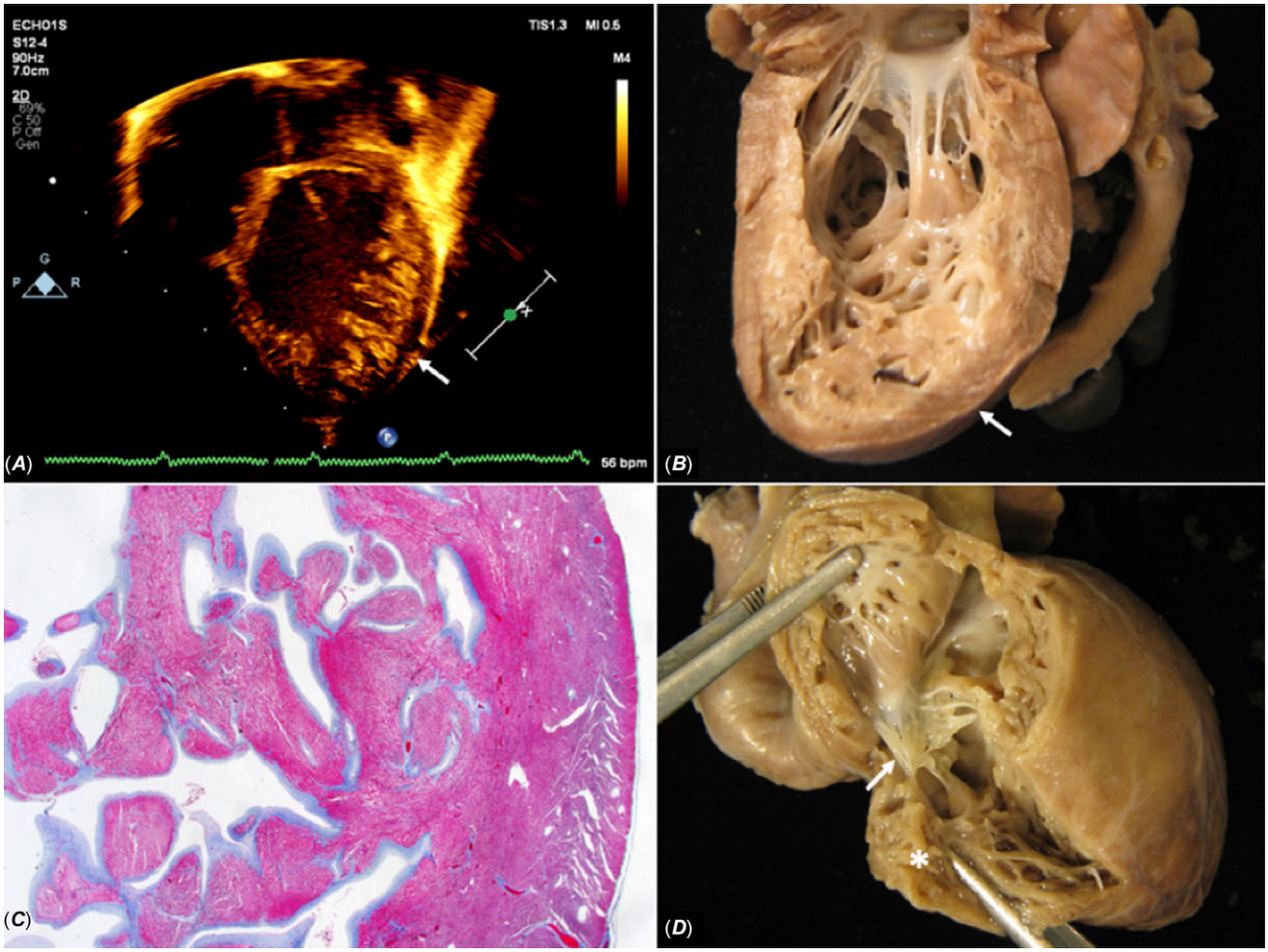

Figure 1. (A) Echocardiogram shows marked hypertrabeculation of the non-compacted layer of the left ventricular myocardium that appears at least three times thicker than the compacted outermost layer of the myocardium (arrow). (B) Postmortem examination of the heart confirmed the imaged left ventricular features. (C) Prominent endocardial fibroelastosis (blue layer) lined the myocardial trabeculae (Masson Trichrome stain, original magnification x 12.5). (D) The right ventricle also shows a non-compacted myocardial layer (*). Additionally, a hypoplastic tricuspid valve (arrow) and reduced right ventricular chamber size are observed.

chamber was relatively small and did not extend to the apex while the left ventricle was dilated with rightward bulging of the ventricular septum. Histologically, there was evidence of patchy cardiomyocyte hypertrophy and marked endocardial fibroelastosis, especially in the non-compacted areas of the myocardium (Fig 1C).

In light of the clinical and autopsy findings, the patient's demise was attributed to circulatory failure due to non-compaction cardiomyopathy, associated with a novel *non-POU domain-containing octamer-binding gene* variant, with extracardiac manifestations of circulatory failure in multiple organs, and superimposed acute pneumonia.

Discussion

The *non-POU domain-containing octamer-binding gene* is located on chromosome Xq13.1 and is a member of the Drosophila behaviour/human splicing protein family involved in various aspects of ribonucleic acid metabolism such as transcriptional regulation and messenger ribonucleic acid splicing.[1] The 11 previously reported pathogenic *non-POU domain-containing octamer-binding gene* variants have been associated with developmental delay, facial dysmorphism, macrocephaly, left ventricular non-compaction cardiomyopathy, and cerebral findings including a thickened corpus callosum in 17 cases (see Table 1).[1–5] A wide spectrum of pathogenic variants, including nonsense, partial deletion, frameshift, and splice variants, has been reported as disease-causing and is consistent with a loss-of-function mechanism.[6] The majority of the cases reported in the literature, as seen in the table, was found to have a de novo or maternally inherited *non-POU domain-containing octamer-binding gene* variant with most mothers reportedly asymptomatic, except for one heterozygous mother with a learning disability.[6] In our case, the patient´s mother was a healthy and asymptomatic mosaic for the p.R256I variant in the *non-POU domain-containing octamer-binding gene* leading to a missense variant c.767G>T in exon 8, a conserved region, in the *non-POU domain-containing octamer-binding gene* of the patient. MutationTaster and Combined Annotation Dependent Depletion indicated that the variant is predicted to be disease-causing with possible protein and splice site changes (Amino Acid change score of 97) and a Combined Annotation Dependent Depletion score of 31. However, according to the

https://doi.org/10.1017/S1047951121004923 Published online by Cambridge University Press

Table 1. Clinical and genetical overview of the *NONO* variants reported in the literature

Study	Patient age and ethnicity	*NONO* variant (NM_001145408) and inheritance	Cardiac anomalies	Neurologic and brain anomalies	External features
Mircsof et al (2015)	17-year-old male Caucasian	c.1131G>A; p.(Ala377), splice site variant, *de novo*	Normal cardiac ultrasound at 9 years	Developmental delay, intellectual disability, elocution disability, thick corpus callosum, small cerebrum	Macrocephaly, elongated face, malar hypoplasia, short palpebral fissures, high-arched-palate
	15-year-old male Caucasian	c.1394dup; p.(Asn466Lysfs*13), one-base-pair insertion, maternally inherited	NR	Intellectual disability, elocution disability, hypotonia	Macrocephaly, elongated face, short forehead, upslanting palpebral fissures, malar hypoplasia
	20-year-old male Caucasian	c.1093C>T; p.(Arg365*), nonsense variant	NR	Intellectual disability	NR
Reinstein et al (2016)	17-year-old male Caucasian	c.1171 + 1G>T, splice donor, *de novo*	LVNC	Global development delay, autism, intellectual disability, verbal dyspraxia, hypotonia, hypoplastic corpus callosum with underdeveloped splenium	Macrocephaly, elongated face, prominent nose, wide mouth, thick vermilion
Scott et al (2017)	10-year-old male Hispanic	c.1093C>T, p. Arg365*, *de novo*	LVNC, RVH, ASD, VSD, PDA	Global development delay, mild truncation of the splenium of the corpus callosum	Macrocephaly, plagiocephaly, elongated face, bilateral epicanthal folds, down-slanted palpebral fissures, accessory nipples
	5-year-old male Hispanic	c.1394dupC, p. Asn466Lysfs*13, *de novo*	LVNC, ASD, VSD, PDA	Global development delay, hypotonia	Macrocephaly, elongated face, frontal bossing, malar hypoplasia, café au lait and hypopigmented macules
	15-month-old male Hispanic	Maternal Xq13.1 deletion involving the first three coding exons of NONO	LVNC, PFO, cardiac transplant	Global development delay, hypotonia, underdeveloped corpus callosum, persistent cavum septum pellucidum, dilated right ventricular system	Macrocephaly, frontal bossing
Carlston et al (2019)	2-year-old male Caucasian	c.154 + 5_154 + 6delGT, p. Asn52Serfs*6, Maternally inherited	LVNC, EA, PFO	Global developmental delay, mild pseudobulbar palsy, hypotonia, thick corpus callosum, Chiari I malformation, flattened pituitary	Macrocephaly, triangular face, widely spaced eyes, down-slanted palpebral fissures, malar hypoplasia, thin vermilion of the upper lip
Sun et al (2020)	Fetus	c.154 + 9A>G, p. Asn52Serfs*3, Maternally inherited	HLHS, MV dysplasia, aorta hypoplasia	NR	NR
Sun et al (2020b)	Fetus A1	c.246_249del, p. Pro83Thrfs*7, frame-shift, X-linked recessive	Biventricular non-compaction, EA, PS, VSD, pericardial effusion	NR	NR
	Fetus A2	c.246_249del, p. Pro83Thrfs*7, frame-shift, X-linked recessive	LVNC, PA, VSD, aorta astride, right aortic arch, pulmonary dysplasia, transposition of the aorta, PLSVC	NR	NR
	Fetus A3	c.246_249del, p. Pro83Thrfs*7, frame-shift, X-linked recessive	LVNC, PS, VSD, right ventricular diverticulum, PLSVC	NR	NR
	Fetus B1	c.471del, p. Gln157Hisfs*18, frameshift variant, X-linked recessive	LVNC, Ebstein anomaly, PS, ASD, variation of branch of aortic arch	NR	NR
	Fetus B2	c.471del, p. Gln157Hisfs*18, frameshift variant, X-linked recessive	Biventricular non-compaction, EA, PS, VSD	NR	NR

(*Continued*)

https://doi.org/10.1017/S1047951121004923 Published online by Cambridge University Press

Table 1. (*Continued*)

Study	Patient age and ethnicity	*NONO* variant (NM_001145408) and inheritance	Cardiac anomalies	Neurologic and brain anomalies	External features
Sewani et al (2020)	2-year old male Hispanic	c.550C>T, p.(Arg184*) maternally inherited	LVNC, ASD, VSD, PDA, aortic dilation	Global developmental delay, hypotonia,	Macrocephaly, elongated face, frontal bossing, upslanting palpebral fissures, epicanthal folds, large ear lobules, depressed nasal root, inverted nipples, Mongolian spots on back
	4-year old male Caucasian	c.1171 + 1G>A, splice site, *de novo*	Increased concentric left ventricular wall thickness with some features of LVNC	Global developmental delay, hypotonia, dysplastic corpus callosum, cavum septum pellucidum, cavum vergae	Macrocephaly, slanted palpebral fissures, mild ptosis
	White male fetus miscarried at 16 weeks of gestation	c.457C>T, p.(Arg153*) stop-gain variant, *de novo*	Cardiomegaly, pulmonary stenosis	NR	Hypertelorism, retrognathia, low set ears
This study	3-month-old male Caucasian	c.767G>T, p. Arg256Ile, missense variant, maternally inherited	Cardiomegaly, biventricular non-compaction, tricuspid hypoplasia, PFO, Endocardial fibroelastosis	Normal brain MR*	Dysmorphic craniofacial features including widened appearance of the head and widened inter-canthal distance

ASD: atrial septal defect; HLHS: hypoplastic left heart syndrome; LVNC: left ventricular non-compaction; MV: mitral valve; NR: not reported; PA: pulmonary atresia; PDA: patent ductus arteriosus; PFO: patent foramen ovale; PLSVC: persistent left superior vena cava; PS: pulmonary stenosis; RVH: right ventricular hypertrophy; VSD: ventricular septal defect.
*The findings of the decedent's brain were non-specific and likely a result of the hypoxic conditions secondary to cardiac dysfunction. Furthermore, previous patients reported with *NONO*-related brain deformities all had normal brain MRI during infancy, however, when a repeat MRI was performed at the earliest 10 months of age or older, clear deformations of the corpus callosum was detected.

American College of Medical Genetics guidelines, functional studies and additional reports of the variant are needed in order to be more definitive in regard to the pathogenicity of the variant.

Non-compaction cardiomyopathy, also known as left ventricular non-compaction cardiomyopathy, is a rare and more recently recognised type of cardiomyopathy characterised by the presence of excessive trabeculations and deep intratrabecular recesses typically involving the left ventricle but can also involve the right ventricle or both ventricles. Although diagnostic criteria vary, a>2:1 ratio of non-compacted:compacted myocardium is often used.[7] The genesis of this specific type of cardiomyopathy is thought to be an arrest of the final stage of normal myocardial morphogenesis, leading to a thick non-compacted inner myocardial layer and a thinner compacted outer myocardial layer. Left ventricular non-compaction cardiomyopathy is often associated with other findings such as arrhythmias, left ventricular dilation and/or hypertrophy, systolic and/or diastolic dysfunction, and it has previously been associated with various forms of CHD with right-sided lesions such as Ebstein anomaly, pulmonic stenosis, and pulmonary and tricuspid atresia being the most frequent.[8]

Disease severity and outcome vary by phenotype, with isolated left ventricular non-compaction cardiomyopathy considered relatively benign while the hypertrophic and dilated left ventricular non-compaction cardiomyopathy are associated with an increased risk of mortality.[8] The clinical presentation varies from asymptomatic to congestive heart failure, atrial and ventricular arrhythmias, thromboembolic events, and sudden cardiac death. Both sporadic and familial left ventricular non-compaction cardiomyopathy have previously been reported, with a family history present in up to 50% of patients, usually with a X-linked recessive or an autosomal dominant with incomplete penetrance pattern of inheritance.[9]

The hereditary left ventricular non-compaction cardiomyopathy is usually caused by mutations in genes encoding for sarcomeric or cytoskeletal proteins such as myosin heavy chain 7, *myosin-binding protein C,* and titin, and most of the involved genes are also found in other forms of hypertrophic and dilated cardiomyopathy.[8] In adults with ventricular non-compaction, there is a dominance of left ventricular involvement; however, fetal and neonatal cases are frequently found to have biventricular involvement. A study by Tomar et al showed a decrease of the right ventricular non-compaction severity and an improvement of right ventricular function in a 6-week postnatal follow-up while the left ventricle remained the same.[10] The higher incidence of right ventricular involvement in fetal ventricular non-compaction has been hypothesised to be associated with the dominance of the right ventricular during the fetal circulation, which decreases after birth leading to regression of the appearance of non-compaction in the right ventricular.[10] Our patient was 3 months old at the time of demise, and the autopsy findings showed clear signs of biventricular non-compaction, however, with more severe left ventricular hypertrabeculation.

Loss-of-function mutations in the *non-POU domain-containing octamer-binding gene* can lead to transcript deregulation of *GABRA2* and subsequent aberrant function of the gephyrin scaffolding protein in the post-synaptic junctions of *GABA2* inhibitory neurons.[4] No specific mechanism has been attributed to *non-POU domain-containing octamer-binding gene* loss of function mutations in left ventricular non-compaction. However, studies on left ventricular non-compaction cardiomyopathy not associated with

https://doi.org/10.1017/S1047951121004923 Published online by Cambridge University Press

non-POU domain-containing octamer-binding gene variants suggest it may be secondary to digenic variants in *GATA4* and *PTEN* or variants in titin gene.[4] To the best of our knowledge, three prenatal and seven postnatal cases of *non-POU domain-containing octamer-binding gene* variants demonstrating left ventricular non-compaction cardiomyopathy have been reported, suggesting that this phenotype is strongly associated with the *non-POU domain-containing octamer-binding gene* syndrome.[1–3,5,6] Two prenatal cases of *non-POU domain-containing octamer-binding gene* variants have further been reported to have biventricular non-compaction as in our case.[5] However, no previous cases of *non-POU domain-containing octamer-binding gene* variants have been associated with biventricular non-compaction *and* tricuspid hypoplasia as found in our patient. This particular variant found in the decedent (*non-POU domain-containing octamer-binding gene* c.767G>T, p.R256I [NM_001145408]) and the associated congenital anomalies have not previously been reported and therefore expands the reported mutational and phenotypic spectrum that may occur in *non-POU domain-containing octamer-binding gene* mutation-associated disorders.

Acknowledgements. None.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Conflicts of interest. None.

References

1. Carlston CM, et al. Expanding the genetic and clinical spectrum of the NONO-associated X-linked intellectual disability syndrome. Am J Med Genet A 2019; 179: 792–796.
2. Reinstein E, et al. Intellectual disability and non-compaction cardiomyopathy with a de novo NONO mutation identified by exome sequencing. Eur J Hum Genet 2016; 24: 1635–1638.
3. Scott DA, et al. Congenital heart defects and left ventricular non-compaction in males with loss-of-function variants in NONO. J Med Genet 2017; 54: 47–53.
4. Mircsof D, et al. Mutations in NONO lead to syndromic intellectual disability and inhibitory synaptic defects. Nat Neurosci 2015; 18: 1731–1736.
5. Sun H, et al. Characteristics of cardiac phenotype in prenatal familial cases with NONO mutations. Circ Genom Precis Med 2020; 13: e002847.
6. Sewani M, et al. Further delineation of the phenotypic spectrum associated with hemizygous loss-of-function variants in NONO. Am J Med Genet A 2020; 182: 652–658.
7. Abbasi Y, et al. The pathogenicity of genetic variants previously associated with left ventricular non-compaction. Mol Genet Genomic Med 2016; 4: 135–142.
8. Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. Lancet 2015; 386: 813–825.
9. van Waning JI, et al. Genetics, clinical features, and long-term outcome of noncompaction cardiomyopathy. J Am Coll Cardiol 2018; 71: 711–722.
10. Tomar M, Radhakrishnan S. Biventricular noncompaction: a rare cause of fetal distress and tricuspid regurgitation. Images Paediatr Cardiol 2009; 11: 1–5.

https://doi.org/10.1017/S1047951121004923 Published online by Cambridge University Press