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Case Report

Early Lethal Noncompaction Cardiomyopathy in Siblings With Compound Heterozygous *RYR2* Variant

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ABSTRACT

Two siblings presented with early lethal noncompaction cardiomyopathy (NCCM). Both carry compound heterozygous variants in the ryanodine receptor gene (*RYR2*). Evolving animal and human data have begun to implicate a role for *RYR2* dysfunction in the development of NCCM. The identified *RYR2* variants are therefore likely causative for this early lethal NCCM phenotype. Further research is needed to understand the role of *RYR2* in the heart compaction process.

RÉSUMÉ

Deux frère et súur ont présenté une cardiomyopathie par non-compaction létale précoce (NCCM — noncompaction cardiomyopathy). Tous deux sont porteurs de variants hétérozygotes composés dans le gène du récepteur de la ryanodine (*RYR2*). Des données évolutives sur l'animal et l'humain pointent vers le dysfonctionnement de *RYR2* dans la survenue de la NCCM. Les variants *RYR2* identifiés sont donc probablement à l'origine de ce phénotype létal précoce de la NCCM. Des recherches supplémentaires sont nécessaires pour comprendre le rôle du *RYR2* dans le processus de compaction cardiaque.

Noncompaction cardiomyopathy (NCCM) is thought to be caused by an arrest of the compaction of the myocardial musculature during embryogenesis, resulting in the persistence of prominent trabeculae.[1] In most cases, NCCM is diagnosed in adulthood. NCCM is a genetically heterogeneous congenital disorder, and numerous genetic variants have been discovered.[1] The present case report describes 2 siblings with biallelic variants in the ryanodine receptor gene (*RYR2*).

Case Presentation

The first patient was a boy who presented with antenatal bradycardia. Postpartum electrocardiography (ECG) showed sinus bradycardia and prolonged QT interval (520 ms) (Fig. 1A). Echocardiography showed NCCM with decreased systolic and diastolic function (left ventricular end-diastolic diameter [LVEDd] 19 mm, fractional shortening [FS] 26%, left ventricular ejection fraction [LVEF] 40%, and diastolic function: E/A ratio 2.2 [E 0.7 m/s, A 0.31 m/s], pulsed-wave tissue Doppler imaging septal mitral annulus E′ −0.035 m/s, lateral mitral annulus E′ −0.06 m/s, and ratio of noncompacted to compacted myocardium > 2:1). Because of the long QT interval, beta-blocker therapy was initiated. The patient subsequently developed severe bradycardia for which an antibradycardia AAI pacemaker was implanted. At the age of 10 weeks, the patient developed severe low cardiac output and died at the emergency department secondary to cardiogenic shock. No arrhythmias were seen during resuscitation.

After a healthy sibling was born, the third pregnancy was again complicated by fetal bradycardia. Antenatal echocardiography of the second patient was highly suspicious of NCCM. Postpartum ECG showed sinus bradycardia, low T-wave voltages and prolonged QT interval (570 ms) (Fig. 1B). Echocardiography confirmed NCCM and revealed a small ventricular septum defect (LVEDd 20 mm, FS 23%, LVEF 35%, and diastolic function: E/A ratio 2.85 [E 1.06 m/s, A 0.37 m/s], pulsed-wave tissue Doppler imaging septal mitral annulus E′ −0.03 m/s, lateral mitral annulus E′ −0.05 m/s, and ratio of noncompacted to compacted myocardium > 2:1). A subcutaneous loop recorder was implanted for heart rate monitoring and arrhythmia detection. Progressive left ventricular dysfunction was treated with angiotensin-

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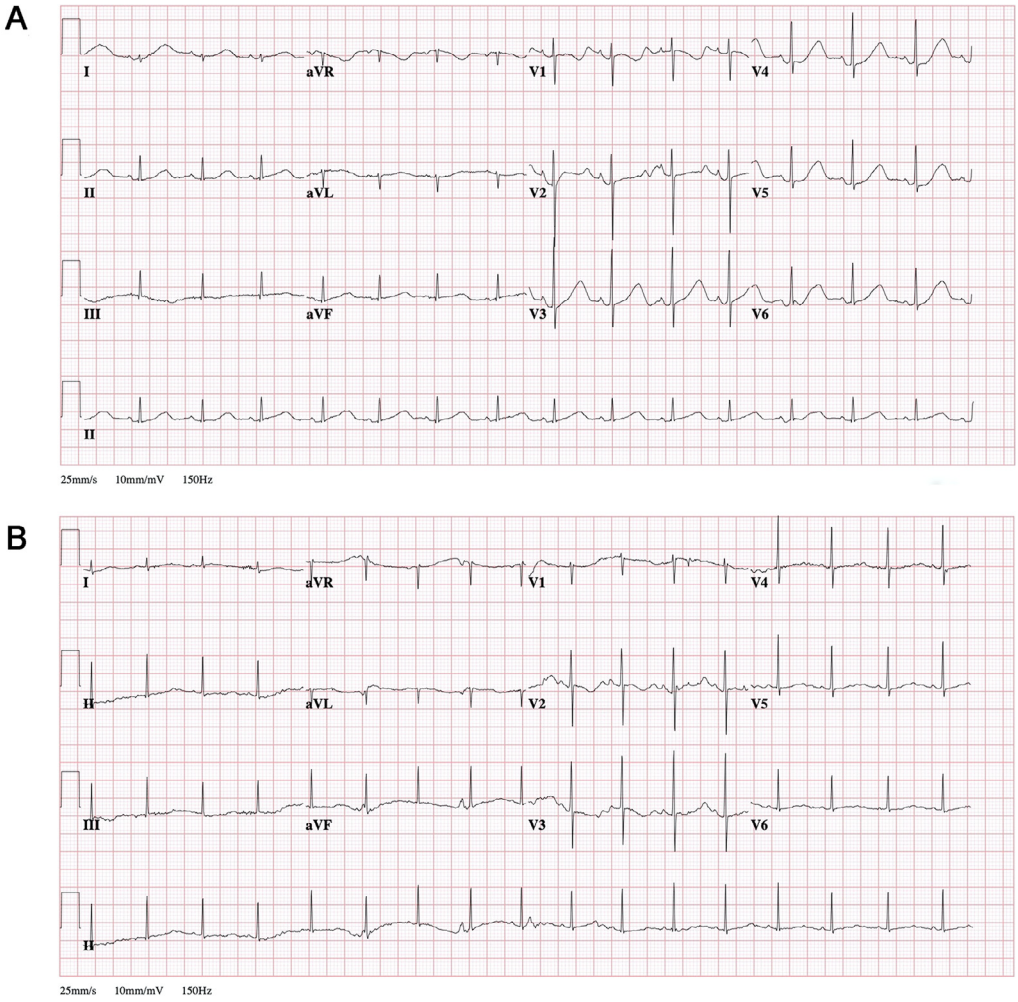

Figure 1. (**A**) Initial electrocardiogram (ECG) of the first patient at age 6 days (25 mm/s, 10 mm/mV) shows sinus bradycardia (89 beats/min) with prolonged QT interval (520 ms). (**B**) Initial ECG of the second patient at age 1 day (25 mm/s, 10 mm/mV). Sinus bradycardia (100 bpm), low T-wave voltages, and prolonged QT interval (570 ms) are present.

converting enzyme inhibitor and diuretics. With progressive dilation of the left atrium, she developed an ectopic atrial tachycardia treated with amiodarone and a beta-blocker. Over time, left ventricular function deteriorated and at the age of 9 months she was admitted with an incessant atrial tachycardia which evolved into a fatal broad complex tachycardia.

Genetic tests showed that both patients carried 2 compound heterozygous variants in *RYR2*. Next-generation sequencing (NGS) identified a heterozygous variant of unknown significance (VUS) in *RYR2* (c.11084T>C; p.(Met3695Thr)), which was not found in gnomAD, and leads to the replacement of a highly conserved amino acid. Copy number variation analysis of the NGS data revealed a heterozygous deletion of exon 19 (c.1827+140_1961+426del), putatively introducing a frame shift, resulting in a null allele secondary to nonsense medicated decay (Fig. 2A). The deletion was confirmed by means of long fragment polymerase chain reaction. Both patients had no dysmorphia or extracardiac anomalies.

The mother proved to be a carrier of the VUS and the father of the exon 19 deletion. The healthy sister carries none of the variants (Fig. 2B). Cardiac evaluation (ECG and echocardiography) showed no conduction abnormalities or ventricular noncompaction in the mother nor in the healthy sibling. Treadmill testing in the mother showed isolated premature ventricular contractions that did not increase during exercise. ECG showed no conduction abnormalities in the father, and echocardiography showed focal trabeculations. Cardiac magnetic resonance imaging showed no evident noncompaction (ratio of noncompacted to compacted myocardium < 2.3:1). Trio whole-exome sequencing of the second patient and the parents did not reveal pathogenic or likely pathogenic variants in any genes implicated in ventricular cardiomyopathy aside from *RYR2*.

With a likely familial cause of the NCCM, prenatal genetic testing was offered during the fourth pregnancy. Chorionic villus sampling showed heterozygosity for the exon 19 deletion (c.1827+140_1961+426del). A healthy girl was born without echocardiographic evidence of left ventricular noncompaction.

Discussion

We report 2 siblings with sinus bradycardia and early lethal NCCM. Both carried 2 compound heterozygous variants in *RYR2*.

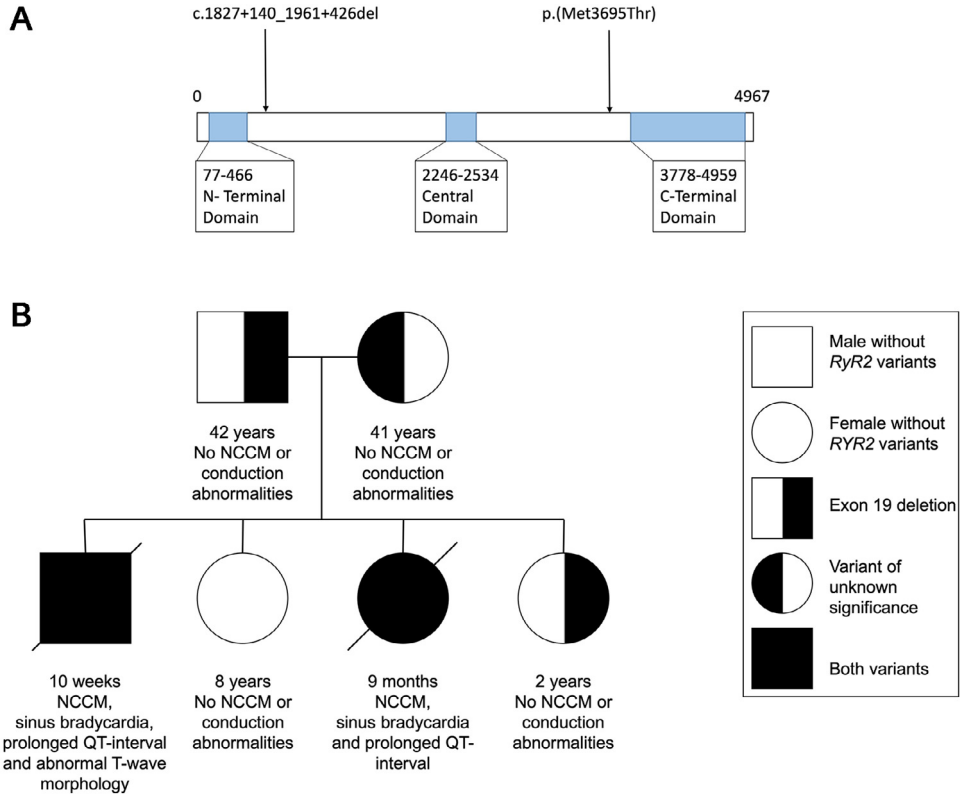

Figure 2. (**A**) Linear depiction of the exon 19 deletion in *RYR2*. (**B**) Family pedigree showing the *RYR2* variants. NCCM, noncompaction cardiomyopathy.

Most pathogenic *RYR2* variants are gain-of-function variants causing catecholaminergic polymorphic ventricular tachycardia, but loss-of-function (LOF) *RYR2* variants may cause life-threatening ventricular arrhythmias.[2] Several reports show a link between in-frame deletions in *RYR2* and NCCM, but the age of onset is usually much later than in the cases reported here.[3,4] Biallelic LOF *RYR2* variants causing NCCM have not been described previously.

RYR2 knock-out mice have cardiomyocytes with high concentrations of Ca^{2+} in the sarcoplasmic reticulum, structurally abnormal mitochondria, trabeculae, and unorganised epicardium and die during embryogenesis. This suggests that *RYR2* is essential for Ca^{2+} homeostasis and normal cardiac development.[5]

In summary, it is likely that compound heterozygosity of the described *RYR2* variants caused the lethal NCCM. The observed sinus bradycardia is hypothesised to be secondary to the impact of *RYR2* dysfunction in the sinus node. The prolonged QT intervals were probably caused by impaired cardiac repolarisation due to the underlying severe NCCM. The early lethal phenotype in these siblings is presumably a result of the *RYR2* missense and LOF variant.

To our knowledge, this is the first case report of compound heterozygous *RYR2* variants leading to early lethal NCCM. Further research is needed to understand the role of *RYR2* in the heart compaction process.

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Disclosures

The authors have no conflicts of interest to disclose.

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