

## Pacing Non-Capture in a Child with Compound Heterozygous SCN5A Mutations

Apinya Bharmanee<sup>1</sup>,  
James M Galas<sup>2</sup>,  
Richard A Humes<sup>2</sup> and  
Harinder R Singh<sup>3</sup>

### Abstract

Mutations in the cardiac sodium channel gene SCN5A are linked to arrhythmias, cardiac conduction defects and cardiomyopathies. We report a 2 year old toddler with symptomatic sinus node dysfunction, negative family history, and increased left ventricular trabeculations. He underwent an unsuccessful attempt at transvenous pacemaker implantation, with no pacing capture at multiple ventricular and atrial sites. He required resuscitation for ventricular fibrillation, and was placed on extracorporeal membrane oxygenation (ECMO) support. Genetic analysis revealed compound heterozygous SCN5A loss-of-function and gain-of-function mutations, individually inherited from both his parents. In addition to the full spectrum of manifestations of SCN5A mutations, our patient also exhibited ventricular inexcitability.

**Keywords:** SCN5A mutation; Compound heterozygous; Pacing non-capture; Inexcitability

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### Case Report

A 27-month old Caucasian boy with a previous history of syncope was referred to cardiology for evaluation of a heart murmur. Previously reported syncopal episodes had been ascribed to breath-holding spells. Family history was negative for sudden death, inherited arrhythmias or the need for pacemakers and defibrillators. His electrocardiograms revealed sinus tachy-bradycardia with accelerated junctional beats, first degree AV block, right ventricular conduction delay, non-specific ST segment changes and QTc ranging between 470 - 510 milliseconds (**Figure 1**). Echocardiography demonstrated increased left ventricular trabeculations with non-compacted to compacted ratio of >2:1 with low normal systolic function. A 24 hour Holter monitor showed heart rates ranging 10-110 beats per minute with an average heart rate of 72 bpm, multiple pauses with the longest pause of 6 seconds and a run of non-sustained wide complex rhythm at a rate of 150 bpm (**Figure 2**). Pacemaker implantation was recommended and the family chose transvenous route of implantation. Cardiac MRI was performed as pacemaker implantation would preclude a study later. The patient underwent general anesthesia by a cardiac anesthetist utilizing sevoflurane, fentanyl and vecuronium during induction. The MRI reported prominent trabeculations in left ventricle however the patient did not meet the MRI criteria for LV non-compaction and no evidence of late gadolinium enhancement.

- 1 Division of Pediatric Cardiology, Simitivej Hospital, Bangkok, Thailand
- 2 Division of Pediatric Cardiology, The Carman and Ann Adams Department of Pediatrics, Children's Hospital of Michigan, Detroit, MI, USA
- 3 Department of Pediatrics, Department of Pediatrics, The Children's Hospital of San Antonio, Baylor College of Medicine, San Antonio, TX, USA

**Corresponding author:**  
Harinder R Singh

✉ Harinder.singh@christushealth.org

Department of Pediatrics, Department of Pediatrics, The Children's Hospital of San Antonio, 315 N San Saba St., Suite 1135, San Antonio, TX 78207, USA.

**Tel:** +12107044789

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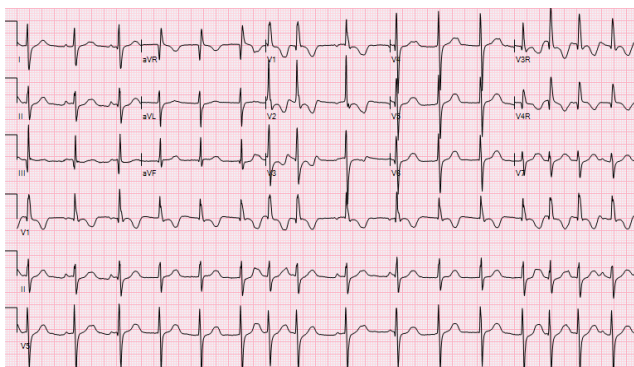
Sinus node function was studied before pacemaker implantation. Baseline electrocardiograms showed sinus bradycardia with intermittent junctional escape rhythm, sinus pauses and intermittent ventricular ectopy. The amplitude of the atrial electrogram was 0.2-0.5 millivolts indicative of atrial quiescence. After multiple attempts to pace the atrium from different sites at maximum output, sinus node recovery time was measured with intermittent capture. Sinus node was significantly depressed with a corrected junctional recovery time of 4.1 seconds. Autonomic blockade revealed an abnormal intrinsic heart rate of 77 bpm (expected 117 beats per minute), suggesting intrinsic sinus node dysfunction. In view of the evidence of atrial standstill and inexcitability, it was decided to implant a single chamber

pacing system with a ventricular lead. Initial attempts to place a ventricular pacing lead (Medtronic 3830-49 cm lead) failed to capture at maximum output from multiple septal pacing sites (x7). The patient developed episodes of bradycardia, asystole and ventricular fibrillation requiring defibrillation and cardiopulmonary resuscitation (CPR). It was then decided to attempt implantation of the pacing lead in the atrium. However, after attempts at multiple atrial sites (x4), no atrial capture was elicited at maximal output. Repeat attempts to pace using a different pacing lead (Medtronic 5076-49 cm) in the ventricle and the atrium were also unsuccessful. Blood gases and electrolytes were stable throughout the procedure. Episodes of asystole and ventricular fibrillation requiring CPR and intermittent defibrillation continued. ECMO support with lidocaine, isoproterenol and dobutamine infusions was initiated during CPR. Echocardiography revealed no pericardial effusion. Even though cardiac function and rhythm stabilized there was evidence of significant neurologic impairment. Following serial neurological evaluations, cardiorespiratory support was withdrawn. The family refused an autopsy, but consented to genetic testing.

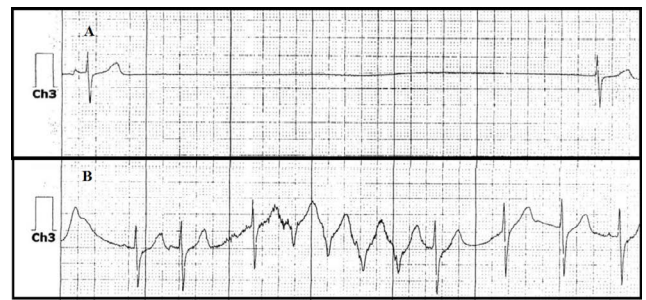
The patient was found to have two disease causing mutations on the SCN5A gene (R104Q and T1645M) as illustrated in **Figure 3**. Subsequently, the parents were tested for the identified mutations. The mother had the R104Q mutation in the SCN5A gene and the father was positive for the T1645M mutation in the SCN5A gene.

## Discussion

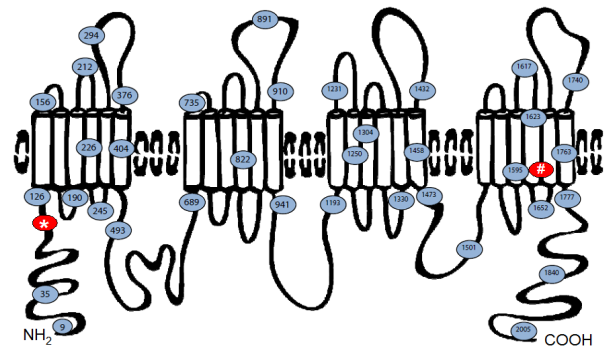
SCN5A gene, located on chromosome 3p21, encodes the alpha subunit of the voltage-gated cardiac sodium channel. It plays a major role in the initial depolarization phase, and determines the conduction velocity and excitability of cardiac myocytes [1,2]. SCN5A mutations have been associated with primary electrical and conduction defects such as Brugada syndrome, long QT3, atrial fibrillation, ventricular fibrillation, sudden infant death syndrome, atrial standstill, sick sinus syndrome and heart block [1,3-5] as well as dilated cardiomyopathy and left ventricular non-compaction [6,7]. Combination of mixed phenotypes can be seen even in the presence of a single SCN5A mutation [8,9].



**Figure 1** 15-lead Electrocardiogram revealed sinus tachy-bradycardia with accelerated junctional beats, first degree AV block (PR 160 ms), right ventricular conduction delay (QRS duration 112 ms), non-specific ST segment changes and Qtc ranging between 470-510 ms (ms-milliseconds).



**Figure 2** Holter monitor tracings: **A.** Asystole with the longest pause of 6 seconds during sleeping. **B.** Non-sustained wide complex rhythm of 4 beats at a rate of 150 beats per minutes.



Adapted with permission from GeneDx

**Figure 3** Cardiac sodium channel (SCN5A) topology demonstrating transmembrane organization, consisting of 4 homologous domains and intracellular amino and carboxyl termini. Examples of loci are marked. \* indicates R104Q mutation previously reported in Brugada syndrome. # indicates T1645M mutation previously reported in Long QT 3 syndrome. (Adapted with permission from GeneDx).

SCN5A mutation expression is related to either loss-of-function or gain-of-function mutations. Both the form of mutations leads to alteration of electrical and mechanical properties of the cells. It is not well understood whether arrhythmias and structural defects are a direct effect of sodium current alterations, or merely secondary to long-standing cardiac abnormalities [9]. Presence of both loss and gain-of-function mutations in an individual may lead to varied phenotypic expressions which, so far, have not been defined.

SCN5A mutation is a prominent known cause for atrial inexcitability. Atrial inexcitability has been reported with compound heterozygous mutation of SCN5A cosegregated with Connexin 40 [10,11] and compound heterozygous loss-of-function mutations [12]. The preferential occurrence of atrial inexcitability in SCN5A mutation, rather than ventricle, may be related to the intrinsic differences between atrial and ventricular myocardium, such as liminal length for action potential propagation, sodium current densities and the speculation that the generation of ventricular action potentials in SCN5A mutation might depend upon sodium channel isoforms other than SCN5A expressed in ventricular

tissue [13,14]. Alternatively, ventricle-specific metabolic or signal transduction events and alternative processing of SCN5A mRNA or accessory proteins other than  $\beta$ -1 and  $\beta$ -3 subunits may enable partial rescue of mutant SCN5A phenotypes in the ventricle but not the atrial myocardium [14].

Our patient had compound heterozygous mutations in the SCN5A gene. Individually, each mutation is a disease-causing mutation. Both are single base pair SCN5A mutations which lead to amino acid substitutions. The R104Q mutation is a loss-of-function mutation, previously reported in a patient with Brugada syndrome [15], whereas the T1645M mutation is a gain-of-function mutation, previously described in long QT3 syndrome patient [16]. The interaction between two pathogenic mutations in a single patient has not been previously reported. Our patient had symptomatic sinus node dysfunction, first degree AV block, right ventricular conduction delay, QT prolongation, atrial quiescence, both atrial and ventricular inexcitability, ventricular arrhythmia and suspicion for LV non compaction, which may also be regarded as an overlap syndrome. Intermittently elevated

ventricular pacing thresholds has been reported in 3/11 patients in a case series with SCN5A loss-of-function mutations associated with poor pacemaker capture [17]. We postulate that the loss-of-function and gain-of-function mutations together may have led to impairment in the action potential generation and/ or propagation in the ventricle as has been reported in the atrium, leading to pacing non-capture in the atrium and ventricle in our patient.

Our report suggests that genetic mutation(s) analysis may have a diagnostic benefit in the etiology of complex cardiac arrhythmias, particularly in the setting of known or suspected cardiomyopathy. Compound heterozygous SCN5A mutation(s) involving both loss-of-function and gain-of-function mutation adds another facet to the spectrum of manifestations.

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