

Novel presentation of *SCN5A* nonsense mutation as *SCN5A* overlap syndrome



Hyo-Jeong Ahn, MD,* So-Ryoung Lee, MD, PhD,* Jangsup Moon, MD, PhD,^{†‡}
Eue-Keun Choi, MD, PhD,*[§] Seil Oh, MD, PhD, FHRS*[§]

From the *Division of Cardiology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [†]Department of Neurology, Seoul National University Hospital, Seoul, Republic of Korea, [‡]Department of Genomic Medicine, Seoul National University Hospital, Seoul, Republic of Korea, and [§]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea.

Introduction

SCN5A is a gene with 28 exons encoding the pore-forming ion-conducting α -subunit of the cardiac voltage-gated sodium channel ($Na_v1.5$).^{1,2} $Na_v1.5$ enables the initiation and propagation of action potentials throughout the myocardium and determines cardiac excitability and electrical conduction.³ Various *SCN5A* mutations have been associated with electrical disorders and equally important structural diseases of the heart: long QT syndrome (LQTS), Brugada syndrome (BrS), isolated conduction defect (Lev-Lenègre syndrome), multifocal ectopic Purkinje-related premature contractions, sick sinus syndrome, atrial fibrillation, and dilated cardiomyopathy. Although originally thought to code for distinct clinical entities, a single *SCN5A* mutation could result in the expression of mixed phenotypes. Therefore, multiple clinical features may coexist within a patient, which is referred to as *SCN5A* overlap syndrome.^{4,5} In this case, we describe a patient with *SCN5A* nonsense mutation (c.664C>T, p.Arg222Ter), previously classified as a pathogenic variant observed in both BrS and individuals tested for LQTS,^{6–8} displaying a wide spectrum of rhythm disturbances in conjunction with familial history.

Case report

A 46-year-old man presented at the emergency department (ED) for repetitive transient cyanosis and agonal respirations during sleep. He was reported to have a transient loss of consciousness and mild epigastric discomfort. Symptoms were relieved after several episodes of vomiting and defecation.

KEYWORDS *SCN5A*; *SCN5A* overlap syndrome; Nonsense mutation; Cardiac sodium channel; Channelopathy
(Heart Rhythm Case Reports 2022;8:209–213)

Funding Sources: The authors have no funding sources to disclose. Conflict of Interest: The authors have no conflicts to disclose. **Address reprint requests and correspondence:** Dr So-Ryoung Lee, Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea. E-mail address: minerva1368@gmail.com.

An electrocardiogram (ECG) showed several transient and different features during acute management at the ED: (1) a sinus rhythm with wide QRS complex followed by coved-type ST-segment elevation and a negative T wave extending into the inferior leads, prolonged PR and QTc intervals (254 ms and 535 ms, respectively), and right bundle branch block (Figure 1A); and (2) a sinus rhythm with narrow QRS complex with frequent premature ventricular complexes presenting superior axis, left bundle branch block pattern, positive lead I and aVL, and negative aVR, thus suspected to originate from right ventricular mid septum or moderator band (Figure 1B).^{9,10} After several hours, ventricular fibrillation (VF) spontaneously developed and was terminated by an external defibrillator shock at 100 J (Figure 1C).

Five years ago, he had experienced dyspepsia, nausea, and dizziness, followed by loss of consciousness with spastic limb movement while on an airplane. A thorough evaluation at the neurology department revealed no abnormal neurological findings. However, 10.5 seconds of sinus pause early in the morning and wide QRS tachycardia were confirmed on 24-hour Holter monitoring (Figure 1D). The minimum heart rate (HR) was recorded as 18 beats per minute (bpm) early in the morning, and the average HR was 52 bpm. Permanent pacemaker implantation was recommended; however, the patient was reluctant to undergo such treatment. Other than this admission history, he had reported no medical problems and was not taking any medication.

On his latest ED visit, serum potassium and magnesium levels were marginally lower than the normal cutoff values: potassium = 3.4 mmol/L and magnesium = 1.3 mEq/L. Coronary angiography and transthoracic echocardiography showed no structural and functional abnormalities, only a mildly dilated left atrium (anteroposterior diameter, 42 mm) and borderline left ventricular end-diastolic diameter (52 mm) were observed. During admission, various ECG abnormalities were observed: doubtful coved-type ST-segment elevation dipping into a negative T wave at right precordial leads (Figure 2A), and saddle-back-type ST-segment

KEY TEACHING POINTS

- We reported a novel clinical presentation of a known pathogenic mutation of *SCN5A* (c.664C>T, p.Arg222Ter) with a family history encompassing various transient electrocardiogram (ECG) features of long QT syndrome, Brugada syndrome, sick sinus syndrome, conduction abnormalities, atrial fibrillation, and marginally increased left ventricular cavity size.
- Several modifiers, including age, sex, and co-inherited genetic variants, may explain the various disease expression and penetrance in overlap syndrome.
- The same genetic variant may be expressed as an entirely different phenotype from one patient to another, requiring different approaches for proper management. Therefore, it is essential to appreciate various surface ECG presentations for accurate diagnosis, risk stratification, and tailored treatment strategies.

elevation followed by a positive T wave (Figure 2B). After a review of his medical history and evaluation results, we decided to implant an implantable cardioverter-defibrillator (ICD) for secondary prevention of sudden cardiac death. The base pacing rate was set at 60 bpm and the patient was discharged after ICD implantation without any medication. Given the consistent prolonged QTc interval during admission, we performed multiple single gene tests (*SCN5A*, *KCNH2*, *KCNQ1*) on initial suspicion of LQTS. Each single gene test consisted of combination of Sanger sequencing and multiplex ligation-dependent probe amplification. A pathogenic variant in *SCN5A* (c.664C>T, p.Arg222Ter, heterozygote) was identified, while no pathogenic/likely pathogenic variant or deletion/duplication was revealed in *KCNH2* and *KCNQ1* at his first scheduled outpatient follow-up. The burden of A/V pacing was 88.4% and <0.1%, respectively, on a printout analysis of the ICD at this visit.

Subsequent ECG and ICD analyses on follow-up revealed another rhythm disturbance. Although the patient was asymptomatic, paroxysmal atrial fibrillation (AF) was seen with a maximum duration of 22 minutes and a burden of <0.1% (Figure 2C). A low dose of beta blocker (bisoprolol 2.5 mg once daily) was added on subsequent follow-up. Taking the patient's various ECG manifestations together—sinus

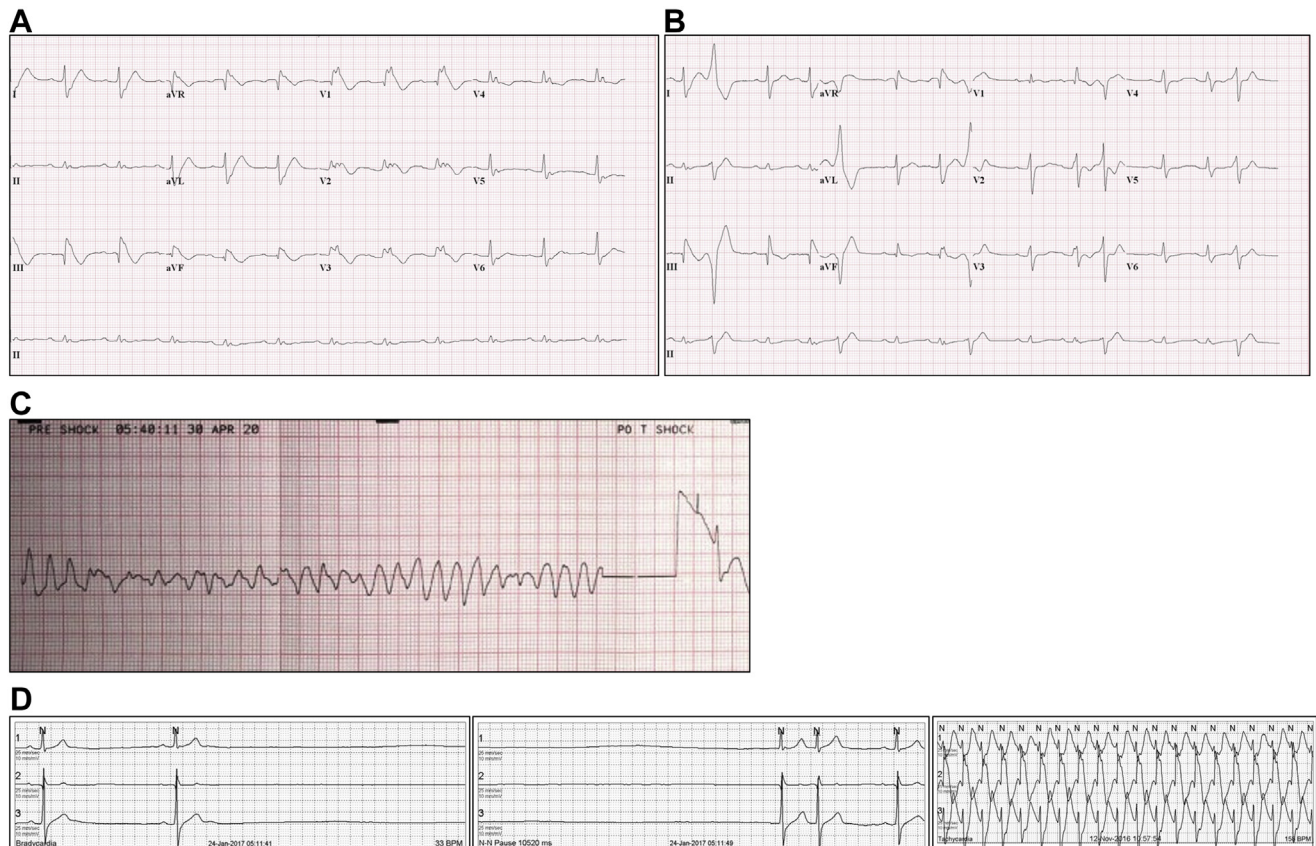


Figure 1 Various electrocardiogram presentations in 1 patient with *SCN5A* variant (c.664C>T, p.Arg222Ter) during initial evaluation: **A**: sinus rhythm with right bundle branch block, prolonged PR and QTc intervals; **B**: frequent premature ventricular complexes; **C**: ventricular fibrillation; and **D**: sinus pause with wide QRS tachycardia.

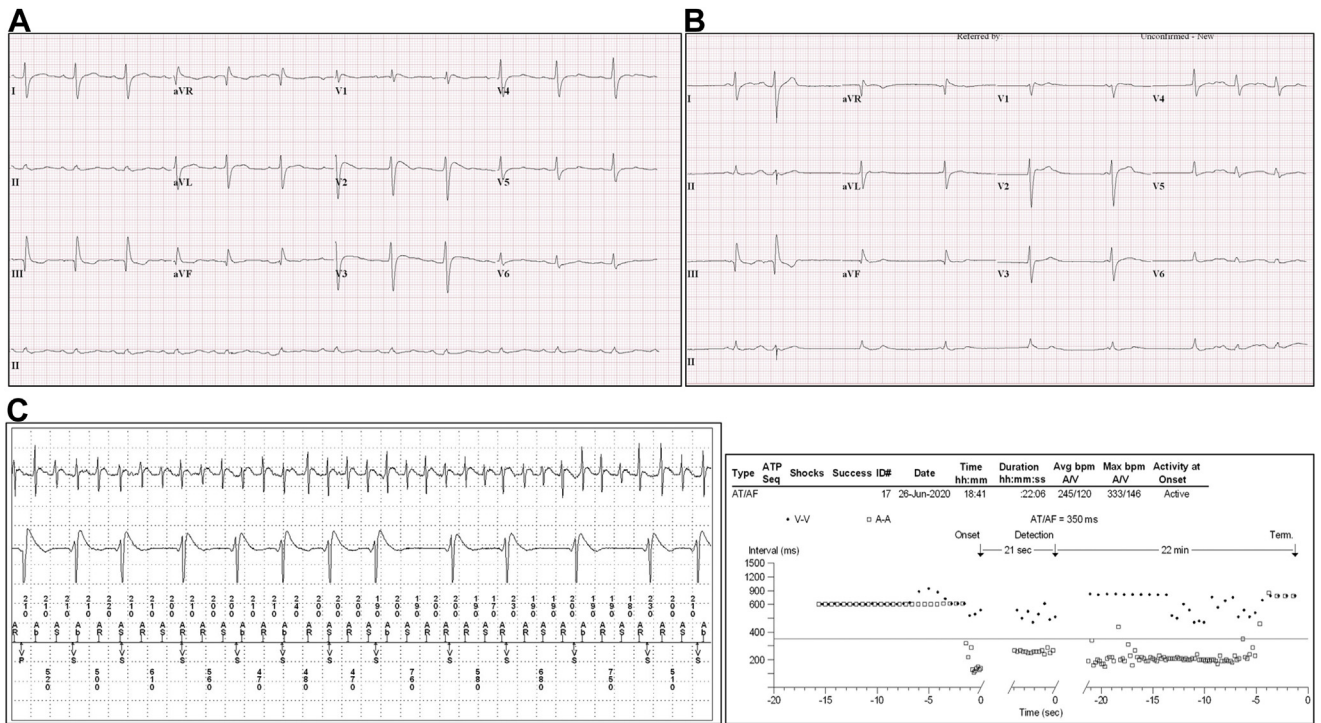


Figure 2 Various electrocardiogram presentations in 1 patient with *SCN5A* variant (c.664C>T, p.Arg222Ter) during follow-up: **A**: type I Brugada pattern, **B**: type II Brugada pattern, and **C**: atrial fibrillation.

node dysfunction with bradycardia, various conduction defects, intermittent prolonged QT interval, Brugada signature ECG, AF, and ventricular arrhythmia (VF)—we were able to diagnose him with *SCN5A* overlap syndrome with a known pathogenic nonsense mutation.

In line with his diagnosis, he had a family history of cardiac arrhythmia. His mother in her mid-40s underwent pacemaker implantation owing to sick sinus syndrome. His older brother presented with sinus bradycardia and syncope, but no further electrocardiogram abnormalities were confirmed. His sister presented with sinus rhythm, HR of 61, and concomitant bifascicular block (right bundle branch block and left anterior fascicular block). A targeted genetic test of *SCN5A* was performed on his sister, and a pathogenic variant of *SCN5A* (c.664C>T, p.Arg222Ter, heterozygote) was also discovered. **Figure 3** and **Supplemental Figure 1** illustrate a

pedigree of the family with the individual genetic test and electrocardiogram results of the patient’s brother and sister.

Discussion

In this case, we reported a novel clinical presentation of a known pathogenic mutation of *SCN5A* (c.664C>T, p.Arg222Ter) encompassing various transient ECG features of LQTS, BrS, sick sinus syndrome, conduction abnormalities, AF, and marginally increased left ventricular cavity size. The patient initially complained of vague epigastric discomfort and dizziness but eventually presented with VF years later. During admission, the patient exhibited transient and characteristic ECG features that prompted clinicians to establish the diagnosis. Considering the cardiac evaluation and a genetic test together with the patient’s history, we

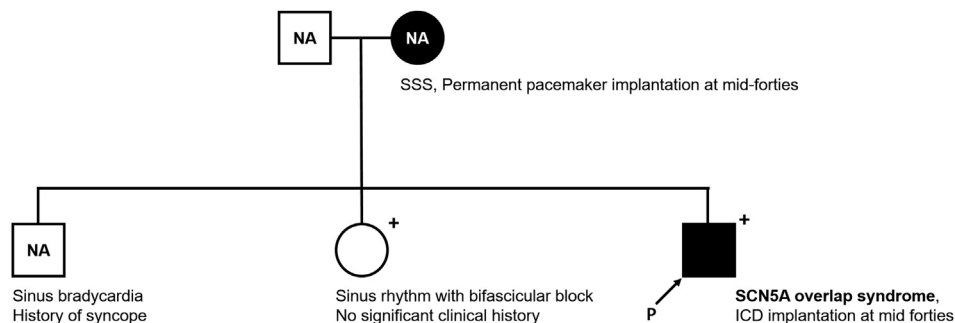


Figure 3 Pedigree and electrocardiograms of the patient’s family. +: *SCN5A* (c.664C>T, p.Arg222Ter) carrier. ICD = implantable cardioverter-defibrillator; NA = not available for genetic information; SSS = sick sinus syndrome.

diagnosed the patient with SCN5A overlap syndrome with a noted nonsense mutation.

In 1999, a multigenerational study of a Dutch family provided the first evidence that a single SCN5A mutation (1795 insD mutation) could result in an overlap syndrome of cardiac sodium channel diseases.^{4,5} In the following years, extensive combinations of phenotypes and related SCN5A mutations have been identified, and several explanations of simultaneously merged manifestations in a single mutation have been suggested. Loss- and gain-of-Na_v1.5-function (representative phenotypes are BrS and LQTS, respectively) features are apparent at different phases of the action potential, and the accompanying disruption of sodium currents varies according to the altered gene function. Depending on the existing HR, the subsequent availability of voltage-dependent sodium channels changes, and the dominant phenotype can be switched from one to the other. This putative underlying mechanism was verified in both computational and mouse models.^{11,12} SCN5A c.664C>T, p.Arg222Ter mutation is a nonsense mutation in exon 6 and is observed in individuals tested for LQTS and 1 with BrS.^{6–8} Although in vitro recapitulation of the patient's mixed phenotypes was not provided, we introduced a case enabling further exploration of SCN5A and interpretation of the cardiac sodium channel.

An intriguing aspect of this clinical vignette is that his first-degree relatives (sister and brother), 1 of which was found to carry the same genetic variant of SCN5A, had no noticeable ECG findings other than sinus bradycardia and clinically insignificant conduction abnormality (bifascicular block). This family demonstrated varying disease severity: asymptomatic mutation carrier (sister), sinus bradycardia with syncope history (brother), sick sinus syndrome with pacemaker implantation (mother), and VF arrest case (index patient). Several modifiers have been investigated to influence the disease expression and penetrance in overlap syndrome. Age, sex, and exogenous factors, such as body temperature or electrolyte disturbances, could be potential clinical determinants of disease.¹³ Moreover, genetic modifiers and coexistence of compound mutations or single nucleotide polymorphisms may contribute to the diverse phenotypes among individuals with the same variant.¹ However, it remains unclear why 1 phenotype predominates or which combination of phenotypes become apparent in a patient with a particular mutation. In this case, we performed Sanger sequencing and multiplex ligation-dependent probe amplification of target genes based on the patient's clinical symptoms. Therefore, any coexistence of compound mutations of single nucleotide polymorphisms could not be evaluated, and confirmation of possible genetic modifiers that might explain varying disease severity in the family is limited.

It is important to appreciate various surface ECG presentations within an individual for accurate diagnosis, risk stratification, and tailored treatment strategies. For example, the risk of lethal ventricular arrhythmias is higher in LQTS

type 3 with the existence of additional multifocal ectopic Purkinje-related premature contractions than in patients with LQTS type 3 alone.¹⁴ In addition, the various diseases stemming from SCN5A mutations have distinct responses to different antiarrhythmic drugs. For example, beta blockers are well known to be efficient for LQTS type 1; mexiletine and ranolazine are considered promising drugs in LQTS type 3; and quinidine is the drug of choice for BrS.¹⁵ The same genetic variant may be expressed as an entirely different phenotype from one patient to another, requiring different approaches for proper management. Therefore, clinicians should not only determine the genetic mutation of cardiac channels present in a patient, but also discern its manifestations for a profound understanding of the disease and delivering optimal care.

Conclusion

We introduced a novel clinical case of a known pathogenic variant of SCN5A (c.664C>T, p.Arg222Ter) displaying various ECG presentations: a VF episode, prolonged QT interval, BrS, sick sinus syndrome, conduction abnormalities, and AF. Moreover, the patient's family showed varying disease expressivity and severity. The clinical spectrum of SCN5A mutations is broad, and patients often exhibit transient ECG abnormalities. Overt diagnostic changes can be missed in concealed and intermittent forms. Therefore, approaching varying ECGs with a high index of suspicion, precise interpretation, and incorporation of molecular study results is of paramount importance in the treatment of cardiac sodium channelopathy patients.

Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrcr.2021.12.014>.

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