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Novel Phenotypic Effects of a Rare *SCN5A* (c.2482C>T) Mutation

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ABSTRACT

In a familial cohort with 8 heterozygous carriers of a rare pathogenic *SCN5A* mutation (c.2482C>T), 4 female mutation carriers manifested with fetal ventricular tachycardia and 2:1 atrioventricular block. One presented with multifocal ectopic premature Purkinje-related complexes-like phenotype and atrial fibrillation later in life. These novel findings inform the need for robust fetal monitoring of mutation carriers. (J Am Coll Cardiol Case Rep 2024;29:102212) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The *SCN5A* gene encodes the alpha subunit of Nav1.5, the main sodium channel in the human heart which is a crucial component of cardiac conduction system.[1,2] We report a multigenerational familial cohort with 8 heterozygous carriers of a rare pathogenic *SCN5A* missense mutation (exon 16, c.2482C>T, p.Leu828Phe) some of whom manifested with fetal 2:1 atrioventricular (AV) block and ventricular tachycardia (VT), and multifocal ectopic premature Purkinje-related complexes (MEPPC)-like phenotype in adulthood.

LEARNING OBJECTIVES

- To recognize that the phenotypic effects of rare/pathogenic *SCN5A* mutations can begin in fetal life and can include previously unreported novel phenotypes, so that these patients can be diagnosed early by using fetal echocardiography.
- To diagnose the phenotypes associated with pathogenic *SCN5A* mutations, such as Brugada Syndrome, long QT syndrome, DCM, MEPPC, isolated cardiac conduction defect (Lenégre disease), AF, sick sinus syndrome, and progressive AV block and recognize that pathogenic *SCN5A* mutations can be associated with opposing effects such as bradycardia and atrial/ventricular arrhythmia in the same patient so that optimum treatment can be provided to these patients.
- To understand that familial screening and investigation are essential to elucidate the full phenotypic spectrum of rare/novel *SCN5A* mutations so that phenotype guided treatment can be provided.

CASE REPORTS

PATIENT 1 (INDEX PATIENT). A 13-month-old asymptomatic girl was noted to have episodic 2:1 AV block (fetal heart rate [FHR] 70-80 beats/min), frequent premature ventricular contractions (PVCs) and nonsustained VT (FHR during VT 200-300 beats/min) in utero at 26 weeks' gestation (**Figure 1**). Her mother (patient 2) was started on nadolol 30 mg twice per day at 30 weeks' gestation, which led to a reduction in fetal arrhythmia burden and restoration of sinus

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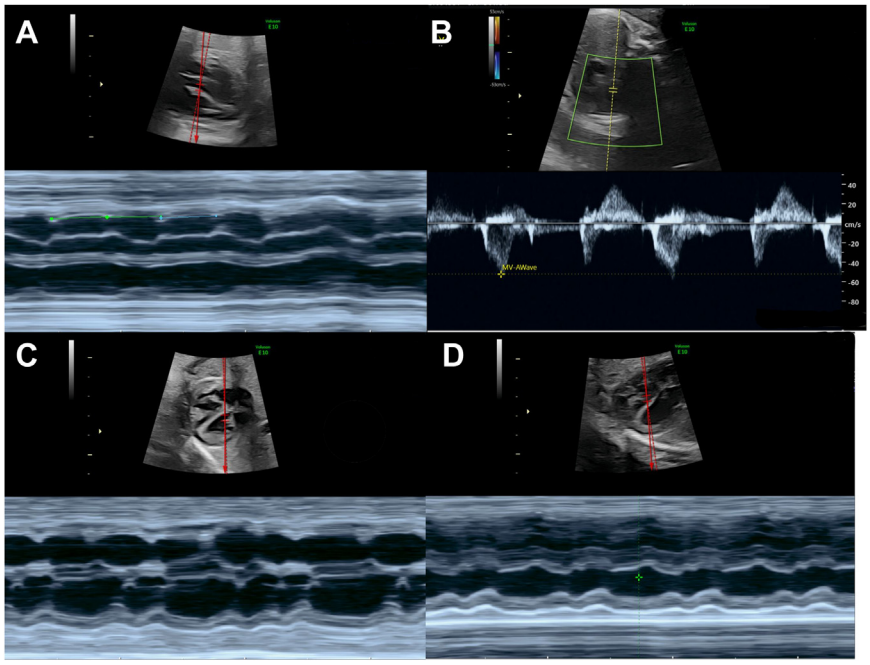
FIGURE 1 Fetal Echocardiographic Findings in Patient 1 (Index Patient)



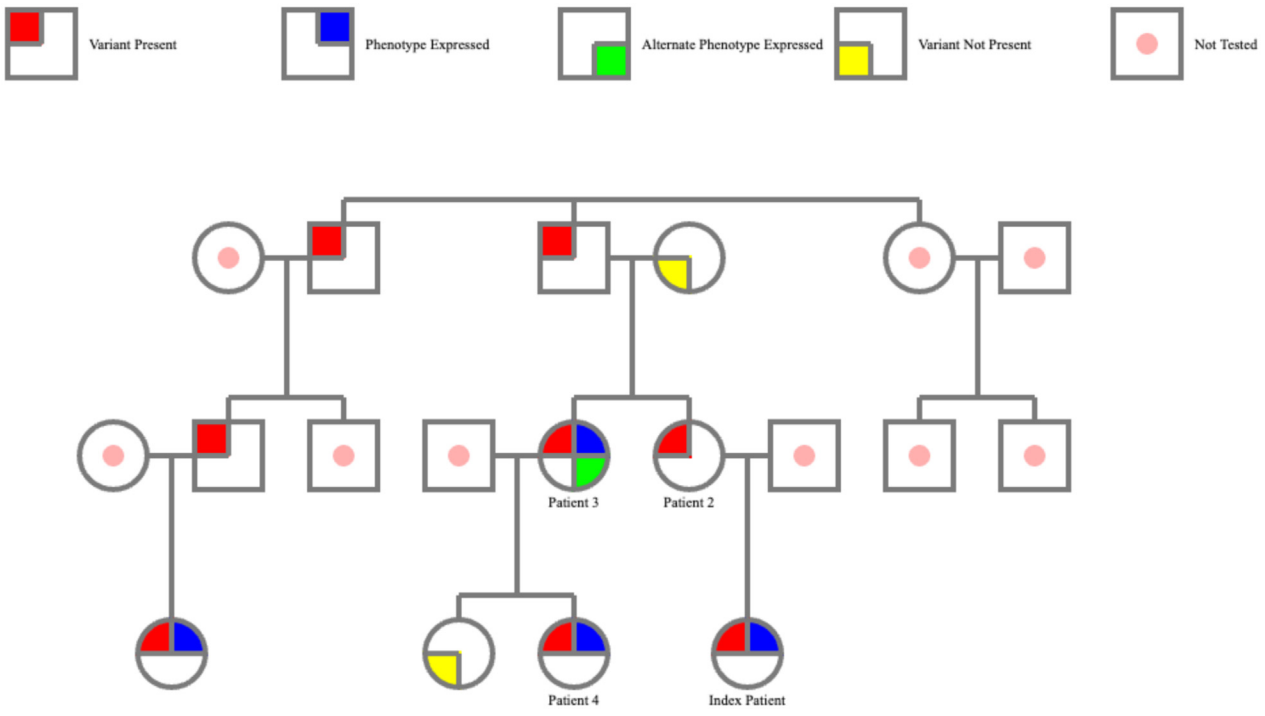
(A) Fetal 2:1 AV block (atrial rate 137 beats/min). (B) Doppler examination of AMC shows 2:1 AV block. (C) Fetal nonsustained VT. (D) Fetal bigeminy. AMC = aortomitral continuity; AV = atrioventricular; VT = ventricular tachycardia.

rhythm. The pregnancy was uncomplicated with normal fetal growth, and she was born at term via cesarean section. She was monitored on telemetry after birth and only occasional atrial ectopy was noted. Her electrocardiogram and echocardiogram were unremarkable. She was started on propranolol (2 mg/kg/d) and did well. Serial Holter monitors and electrocardiograms revealed normal findings, except for a few short runs of ectopic atrial rhythm. Propranolol was therefore discontinued at 2 months of age. Genetic testing (Invitae Arrhythmia and Cardiomyopathy Panel) showed her to be a heterozygous carrier of the familial *SCN5A* mutation (Figure 2).

PATIENT 2 (MOTHER OF THE INDEX PATIENT). A 30-year-old woman was noted to have FHR irregularity on obstetric ultrasound examination performed at 26 weeks' gestation. Serial fetal echocardiograms revealed 2:1 AV block (FHR 70-80 beats/min) and frequent PVCs and nonsustained VT (FHR during VT 200-300 beats/min) (patient 1). She was started on nadolol 30 mg twice per day at 30 weeks' gestation for treatment of fetal arrhythmia. Her echocardiogram, electrocardiogram, and Holter monitors revealed a few short runs of ectopic atrial rhythm (Figure 3). Genetic testing during pregnancy showed her to be a heterozygous carrier of the familial *SCN5A* mutation (Figure 2).

PATIENT 3 (INDEX PATIENT'S MATERNAL AUNT, PATIENT 2'S SISTER). A 34-year-old woman presented with a history of palpitations. She also had a history of fetal arrhythmia. Her electrocardiogram showed junctional rhythm with polymorphic PVCs (Figure 4). Her echocardiogram was unremarkable. She was started on nadolol 30 mg twice per day initially and evaluated with a Holter monitor which showed 2% atrial fibrillation (AF) burden. Frequent polymorphic PVCs were noted (isolated 17.2%, couplets 3.6%, triplets 1.8%). In addition, 184 VT runs (mostly polymorphic) occurred with a maximum rate of 210 beats/min (Figure 5). Given the Holter findings, flecainide 75 mg twice per day was added to nadolol. A Holter was repeated 4 weeks after addition of

FIGURE 2 **Family Pedigree Tree**



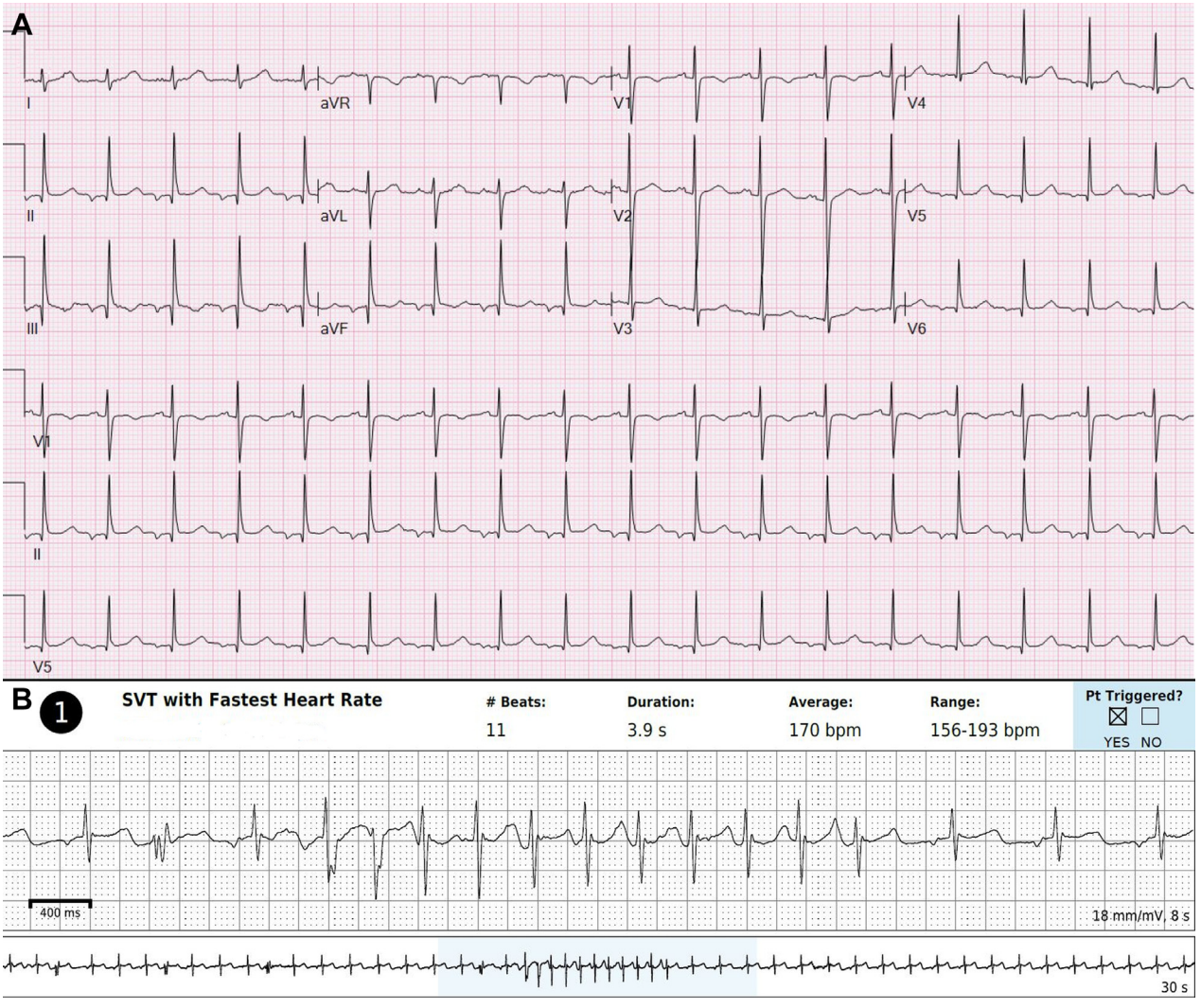
Family pedigree chart shows mutation carriers (red), fetal 2:1 AV block and nonsustained VT (blue), and multifocal ectopic premature Purkinje-related complexes [MEPPC]-like phenotype) and AF (green). Circles represent females and squares represent males. AF = atrial fibrillation; other abbreviations as in Figure 1.

flecainide and showed marked reduction in PVCs and no AF. Upon 18 months of follow-up, the patient is doing well with a marked decrease in her symptoms. She was also found to be a heterozygous carrier of the familial *SCN5A* mutation.

PATIENT 4 (INDEX PATIENT'S COUSIN, PATIENT 3'S DAUGHTER). A 9-year-old girl presented with a history of fetal nonsustained VT and 2:1 AV block. Her genetic testing showed her to be a heterozygous carrier of the familial *SCN5A* mutation. She was also a heterozygous carrier of two polymorphisms: *KCNE1* (exon 4, c.112G>A, p.Gly38Ser) and *KCNH2* (exon 11, c.2690 A>C, Lys897Thr). At 22 weeks' gestation, she was noted to have abnormal rhythm on fetal echocardiogram with periods of 2:1 AV block and rapid nonsustained VT. Suspecting fetal long QT syndrome and Torsade, her mother (patient 3) was started on nadolol and mexiletine, which normalized the patient's rhythm. After delivery, an electrocardiogram was performed, which showed a prolonged QTc of 525 ms. She was started on propranolol after birth and closely monitored. Her QTc normalized by 6 weeks of age, at which time propranolol was stopped. Since then, she has done well and has been asymptomatic from a cardiovascular standpoint. Her recent electrocardiogram and echocardiogram have been normal and her Holter only showed a few short runs of ectopic atrial rhythm.

Patient 2 and 3's father was found to be a heterozygous carrier of the familial *SCN5A* mutation. He also carries a variant of uncertain significance in *MYOM1* (c642_659del, p.Thr215_Ser220del, heterozygous). The father's brother's son (patient 2 and 3's paternal cousin), recently had a daughter who also developed 2:1 AV block and nonsustained VT in utero. However, the family reports that she did well after birth and is currently not on any treatment. This girl and her father carry the familial *SCN5A* mutation. The father has no symptoms. The girl's paternal grandfather has not undergone genetic testing, but is an obligate carrier based on the family history. He has a history of

FIGURE 3 Electrocardiographic and Holter Findings in Patient 2



(A) Patient 2's 12-lead electrocardiogram shows ectopic atrial rhythm. (B) A short run of ectopic atrial rhythm/tachycardia is noted on the Holter.

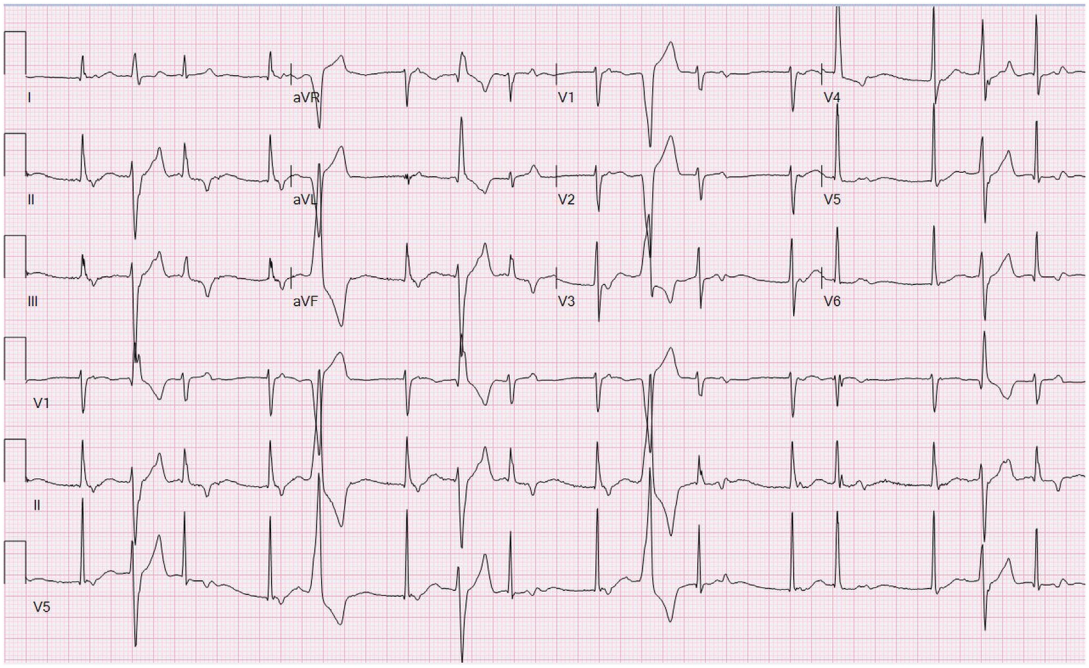
palpitations and is currently being treated with a beta-blocker. The girl's paternal uncle and patient 2 and 3's paternal aunt have not been evaluated or tested (Figure 2).

DISCUSSION

SCN5A mutations are associated with a myriad of cardiac phenotypes which are associated with a loss of SCN5A function (eg, Brugada syndrome) or gain of SCN5A function (eg, long QT syndrome).[1,2] In addition, overlap syndromes have also been reported in *SCN5A* mutation carriers.[2] Moreover, variable phenotypes can be expressed in different individuals who carry the same *SCN5A* mutation.[3] Although this phenotypic variability is not well-understood, it is theorized that the factors such as gender (female and male predisposition to conduction disorder and Brugada syndrome, respectively) and age (exacerbation of cardiac conduction abnormalities with age)[2] may play a role.

The pathogenic *SCN5A* mutation (exon 16, c.2482C>T, p.Leu828Phe) results in a sequence change that replaces neutral nonpolar leucine with

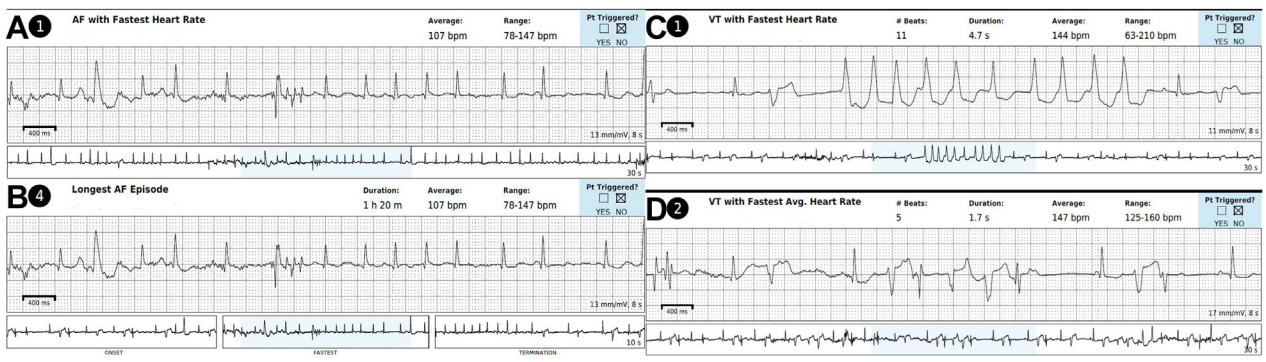
FIGURE 4 **Multifocal Ectopic Premature Purkinje-Related Complexes (MEPPC)-Like Phenotype in Patient 3**



Patient 3's 12-lead electrocardiogram shows junctional rhythm with polymorphic premature ventricular contractions with a right and left bundle branch block pattern.

phenylalanine at codon 828. Four females in our cohort manifested with a severe fetal phenotype consisting of 2:1 AV block, PVCs, and nonsustained VT, which resolved near term. To the best of our knowledge, this phenotype has not been reported previously. A 34-year-old woman presented with polymorphic PVCs, nonsustained polymorphic VT, and AF with excellent therapeutic response to flecainide, suggesting gain of SCN5A function. This variant has been reported previously in a 24-year-old

FIGURE 5 **Abnormal Holter Findings in Patient 3**



Holter findings in patient 3. (A and B) AF. (C and D) Polymorphic PVCs and nonsustained runs of polymorphic VT. Abbreviations as in Figures 1 and 2.

Caucasian woman who manifested with dilated cardiomyopathy (DCM), multifocal PVCs originating from the Purkinje system, and nonsustained VT.[4] She was started on flecainide and, like our patient, had excellent response with complete resolution of ectopy.[4] This mutation was also found in her mother, who also had PVCs and DCM[4] and has been reported in another patient with DCM.[5]

Human *SCN5A*, located on chromosome 3p21, is composed of 28 exons with exon 16 being one of the larger exons (350 base pairs).[6] Exon 16 encodes for the loop region of DII and transmembrane domains 4, 5, and 6.[7] As many as 39 small deletions and missense mutations (some deleterious) have been identified in this region.[7] However, the *SCN5A* missense mutation (exon 16, c.2482C>T, p.Leu828Phe), which lies close to the S4 segment of SCNA5 domain II,[4] and was present in our multi-generational cohort has not been reported in population databases (gnome AD, ExAC).

Two *SCN5A* mutations p.(Arg222Gln)[8] and p.(Arg225Pro),[9] which reside in homologous positions of the voltage-sensor region (S4 segment, domain I) of the cardiac SCN5A, have been identified in patients with MEPPC. Onset of ectopy has been reported in utero in patients with MEPPC; however, AV nodal function tends to be normal. It is noteworthy that all 3 *SCN5A* mutations [p.(Arg222Gln),[8] p.(Arg225Pro),[9] and c.2482C>T (p.Leu828Phe)] are associated with a leftward shift of voltage-dependent activation with resultant triggering of inward sodium current channels at more negative resting membrane potentials.[4] This can facilitate PVCs in fascicular and Purkinje fibers in which sodium ion channels are more abundantly expressed compared to ventricular myocytes.[4]

It is known that *SCN5A* has distinct fetal and adult isotopes which are differentiated by the splicing of exon 6. The fetal isotope has been identified as 6A and the adult as 6B. There is an increase in the expression of the adult variant with age, with the lowest expression being from the fetal period through 4 months of age.[1,10] The fetal isoform of *SCN5A* has been found to demonstrate slower kinetic activation and deactivation as compared with the adult form, as well as a lower depolarization threshold.[1,11] The fetal isoform also displays a greater transient charge influx and slower recovery after activation.[11] *SCN5A* mutations have rarely been associated with fetal abnormalities including sinus bradycardia, AV block, PVCs, and VT.[12] The fetal findings in 4 female members of our cohort suggest that the effects of the familial *SCN5A* variant are likely exacerbated in the fetal SCN5A isotype (6A). The fact that only females in this cohort manifested with fetal findings suggests possible interaction of the mutant *SCN5A* with gender.

CONCLUSIONS

A rare *SCN5A* c.2482C>T (p.Leu828Phe) mutation is associated with a novel fetal phenotype consisting of nonsustained VT and 2:1 AV block and MEPPC like phenotype consisting of polymorphic ventricular and junctional PVCs and AF later in life.

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KEY WORDS **fetal 2:1 AV block, fetal ventricular tachycardia, multifocal ectopic premature Purkinje-related complexes, *SCN5A***