JACC: CASE REPORTS VOL. 4, NO. 5, 2022

CASE REPORT

ADVANCED

CLINICAL CASE SERIES

Noncompaction Cardiomyopathy, Sick Sinus Disease, and Aortic Dilatation

Too Much for a Single Diagnosis?

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ABSTRACT

HCN4 mutations have been reported in association with sick sinus syndrome. A more complex phenotype, including noncompaction cardiomyopathy and aortic dilatation, has recently emerged. We report 3 family members with the pathogenic p.Gly482Arg variant, emphasizing the importance of considering *HCN4* mutations when this combination of features is encountered in clinical practice. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2022;4:287–293)

The hyperpolarization-activated cyclic nucleotide-gated channel 4 (*HCN4*) generates the hyperpolarization-activated "funny" currents that modulate the pacemaker activity in the sinoatrial node.[1] Therefore, mutations in the *HCN4* gene had been primarily associated with sinus bradycardia and sick sinus syndrome; more recently, a more complex phenotype has emerged, including primarily noncompaction cardiomyopathy (NCC), aortic dilatation but also mitral valve defects, early-onset atrial fibrillation, atrioventricular block, and ventricular tachycardia.[2-5]

We report a family with 3 members with the p.Gly482Arg variant in *HCN4* gene, confirming the scarce recent evidence of its association with the combined cardiac phenotype of sinus bradycardia, sick sinus syndrome, NCC, and aortic dilatation.[4,5]

LEARNING OBJECTIVES

- To emphasize that a diverse phenotypic spectrum could be expression of a specific genetic variant even when the gene involved has been historically linked with a different—and maybe more common—clinical presentation.
- To highlight the importance of suspecting the pathogenic variant p.Gly482Arg in *HCN4* gene mutations when sick sinus syndrome, noncompaction cardiomyopathy, and aortic dilatationare detected in clinical practice.
- To stress the importance of performing familial predictive genetic testing and to ensure appropriate surveillance is offered to at risk family members.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received October 29, 2021; revised manuscript received January 7, 2022, accepted January 14, 2022.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2022.01.013

ABBREVIATIONS AND ACRONYMS

ARB = angiotensin receptor blocker

ECG = electrocardiography

HCN4 = hyperpolarization-activated cyclic nucleotide-gated channel 4

ICD = implantable cardioverter-defibrillator

LV = left ventricle

MVP = mitral valve prolapse

NCC = noncompaction cardiomyopathy

This study was approved by our institutional Research Board.

PATIENT 1

The proband in the family (**Table 1, Figure 1**) is a 15-year-old boy who presented with mild pulmonary stenosis and dysplastic pulmonary valve at birth and remained under regular follow-up. During surveillance, he was documented to have asymptomatic sinus bradycardia (**Figure 2A**), left ventricle (LV) NCC, and aortic root and ascending aortic dilatation. His repeated investigations at our institution confirmed his previous findings: a mildly dysplastic aortic valve with mild central regurgitation and no stenosis and mild mitral valve prolapse (MVP) with no significant regurgitation or stenosis (**Figure 3A,** Videos 1 to 4). His cardiac magnetic resonance imaging (MRI) showed mildly dilated (left ventricular end-diastolic volume [LVEDV] 119 mL/m^2), biventricular NCC, good biventricular function (left ventricular ejection fraction [LVEF] 65%, right ventricular ejection fraction [RVEF] 63%), mild aortic root and moderate ascending aortic dilatation (**Figure 4C**). His ambulatory electrocardiographic (ECG) monitoring revealed 66 significant asymptomatic sinus pauses (≥3 seconds, the longest lasting 10.5 seconds), mainly nocturnal, 9 ventricular couplets, and 2 ventricular triplets (**Figure 2B,** Videos 1 to 4). His exercise test showed good chronotropic response, rare supraventricular ectopics, isolated multifocal ventricular ectopics, and occasional bidirectional ventricular couplets (**Figure 5**).

In view of the combination of features, genetic testing was initiated and extended to a large cardiovascular diseases panel (including 405 genes). He was found to be heterozygous for a pathogenic variant in *HCN4* gene (p.Gly482Arg [NM_005477.2:c.144G>A]). No other significant variants were identified.

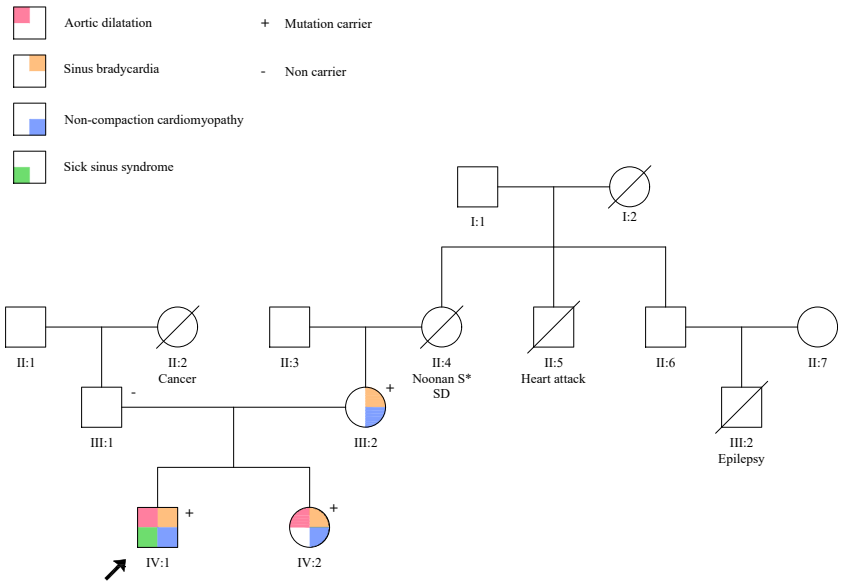
In view of his young age, potential for bradycardic arrest, and possible association of this mutation to ventricular arrhythmias, a primary prevention transvenous dual-chamber implantable cardioverter defibrillator (ICD) was inserted. He was started on a beta-blocker and angiotensin receptor-blocker (ARB) treatment as chemoprophylaxis of further aortic dilatation and to prevent LV remodeling. During follow-up, he has remained asymptomatic, and ICD interrogations have not revealed any arrhythmia.

TABLE 1 Review of the Main Features of the Families With the Pathogenic Variant p.Gly482Arg in *HCN4* Gene Reported in This Article and in Previous Papers

FP	Sex	Age dx (y)	FH SD	Symptoms	HR Rest	Min HR	Max HR	Average HR	SB	SND	NNC	AD	Systolic Function (EF%)	MVP	PM/ICD	Other *HCN4* Gene Variants	Ref. #
AIV.1	M	15	N	N	38	23	153	49	Y	Y	Y	Y	N (70)	Y	ICD PP	N	This study
AIV.2	F	13	N	N	50	38	165	61	Y	ND	Y	Y	N (72)	N	N	N	This study
AIII.2	F	42	N	N	ND	27	ND	ND	Y	ND	Y	N	N (64)	N	N	N	This study
BII.1	F	57	Y	OOHVFA	ND	31	107	62	Y	ND	Y	ND	N (60)	ND	ICD SP	N	(1)
BII.3	F	55	Y	ND	ND	30	103	44	Y	ND	Y	ND	N (64)	ND	N	N	(1)
BII.6	M	54	Y	ND	ND	48	175	85	ND	ND	Y	ND	N (38)	Y	PM	N	(1)
BII.9	F	47	Y	Y	ND	33	102	46	Y	ND	Y	ND	N (61)	ND	PM	N	(1)
BIII.2	M	20	Y	Y	ND	15	126	46	Y	ND	Y	ND	N (50)	ND	PM	N	(1)
BIII.4	M	16	Y	ND	ND	26	110	41	Y	ND	Y	ND	N (73)	ND	PM	N	(1)
CIV.1	M	23	Y	Y	37	21	111	34	Y	Y	Y	ND	N (55)	Y	PM	Y (CSRP3-W4R)	(3)
CIV.2	F	16	Y	Y	36	24	132	38	Y	Y	Y	ND	N (61)	N	N	Y (CSRP3-W4R)	(3)
CIII.2	F	48	Y	N	46	30	118	51	Y	Y	Y	ND	Y (42)	ND	N	Y (CSRP3-W4R)	(3)
DII.1	F	12	Y	N	ND	ND	ND	ND	Y	ND	Y	Y	N	N	N	N	(5)
DII.2	F	18	Y	N	ND	ND	ND	ND	Y	ND	Y	Y	N	N	PM	N	(5)
DII.3	F	24	Y	N	ND	ND	ND	ND	Y	ND	Y	Y	N	Y	PM	N	(5)
EII.1	F	57	ND	ND	40	ND	ND	ND	Y	ND	Y	ND	ND	ND	ND	N	(4)
EII.3	F	55	ND	ND	42	ND	ND	ND	Y	ND	Y	Y	ND	ND	ND	N	(4)
EII.6	M	54	ND	ND	AF	ND	ND	ND	AF	ND	Y	N	ND	ND	ND	N	(4)
EII.9	F	47	ND	ND	38	ND	ND	ND	Y	ND	Y	Y	ND	ND	ND	N	(4)
EIII.2	M	20	ND	ND	30	ND	ND	ND	Y	ND	Y	Y	ND	ND	ND	N	(4)
EIII.4	M	16	ND	ND	39	ND	ND	ND	Y	ND	Y	N	ND	ND	ND	N	(4)
FII.1	F	ND	ND	ND	ND	ND	ND	ND	Y	N	Y	Y	ND	ND	PM	N	(7)
FII.2	M	ND	ND	ND	ND	ND	ND	ND	Y	Y	Y	Y	ND	ND	N	N	(7)
FI.1	M	ND	ND	ND	ND	ND	ND	ND	Y	Y	Y	AA	ND	ND	PM	N	(7)

AA = aortic aneurism; AD = aortic dilatation; Dx = diagnosis; EF = ejection fraction; FH SD = family history of sudden death; FP = family and patient; HR = heart rate; ICD = implantable cardioverter-defibrillator; Max = maximum; Min = minimum; MVP = mitral valve prolapse; ND = not documented; NNC = noncompaction; OOHVFA = out-of-hospital ventricular fibrillation arrest; P = patient; PM = pacemaker; PP = primary prevention; SB = sinus bradycardia; SD = sudden death; SND = sinus node dysfunction; SP = secondary prevention.

FIGURE 1 Pedigree of the Family With the p.Gly482Arg Variant in *HCN4* Gene



Squares = men; **circles** = women. The proband is denoted by an **arrow**. Numbers below the subject symbol indicate the identification of the family members mentioned in the text. Symbols with a **slash** represent deceased subjects. The text below the subject symbol states the cause of death based on medical records or family history. *Clinical diagnosis. S = syndrome; SD = sudden death.

Predictive genetic testing was carried out in the family and revealed that his sister (Patient 2) and mother (Patient 3) are heterozygous for the same variant in *HCN4* gene; his father is negative for this variant. His maternal grandfather is currently considering genetic testing. No additional family members are available for screening at present.

PATIENT 2

A 13-year-old girl (sister of Patient 1) (Table 1), with no relevant cardiac history, was found to be heterozygous for the aforementioned variant in *HCN4* gene. Her cardiac investigations showed sinus bradycardia, borderline aortic dilatation on echocardiogram and mild biventricular dilatation, NNC, and normal systolic function on cardiac MRI (LVEDV 105 mL/m^2, LVEF 74%, RVEDV 111 mL/m^2, RVEF 67%). Her ambulatory ECG monitoring revealed marked sinus bradycardia, with no significant pauses or arrhythmias. She is currently asymptomatic, with no indication for a cardiac device.

PATIENT 3

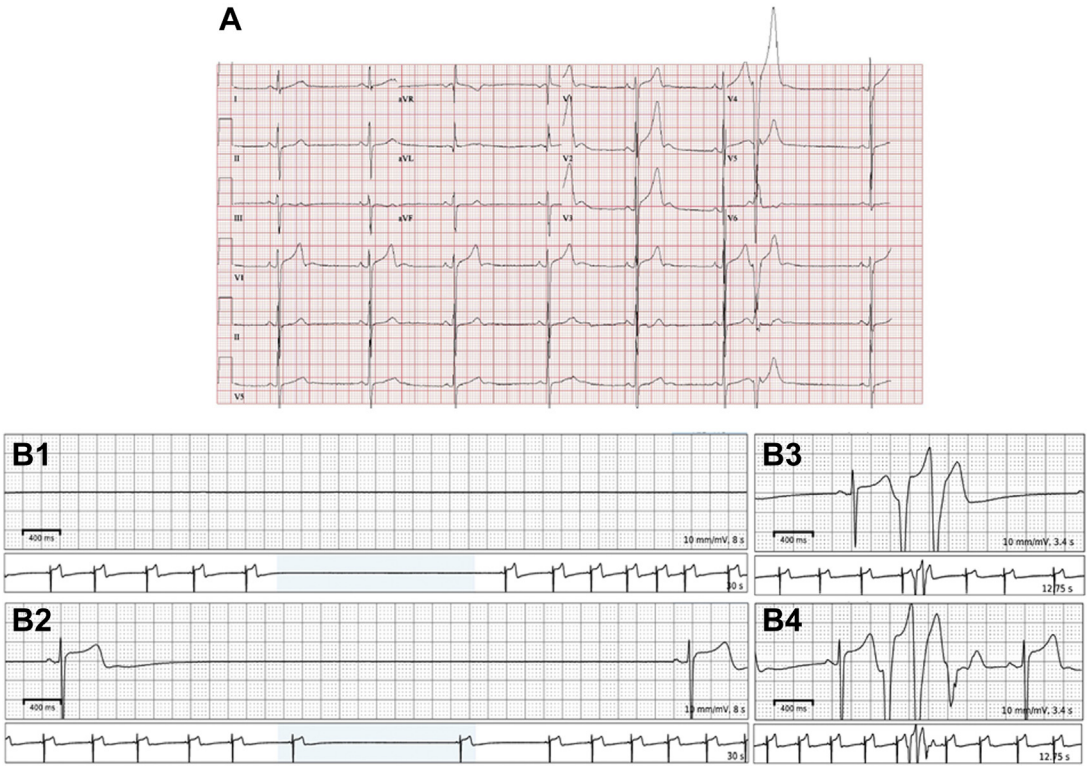
A 50-year-old woman (mother of Patient 1) (Table 1) was assessed for episodes of dizziness at the age of 42 in the context of sinus bradycardia during daytime and a nocturnal pause of 2.3 seconds on an ECG ambulatory monitoring. Symptoms subsided, and she was subsequently discharged from cardiac follow-up. She was found to carry the familial mutation through screening. Her subsequent echocardiogram showed upper normal LV cavity size, apical LV, NCC, and no aortic dilatation. Her ambulatory ECG monitoring revealed frequent periods of sinus bradycardia, a 2.6-second pause, and no significant arrhythmias. In the context of her mutation and sinus bradycardia, she was implanted with a loop recorder for close monitoring of potential sinus pauses or profound bradycardia. To date, she has remained asymptomatic, with no major events.

DISCUSSION

Our study confirms the recently reported association of the combined clinical phenotype of sick sinus syndrome, NCC, and aortic dilatation with the pathogenic variant p.Gly482Arg on *HCN4* gene.[4]

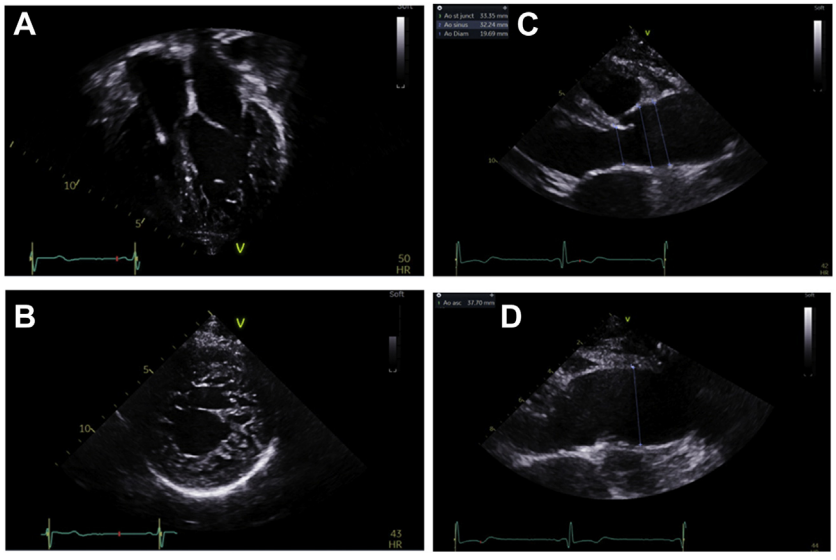
Earliest expression of HCN4 has been reported to be a potential marker for the first heart field.[6] Its expression determines the development of different components and precursors of the cardiac conduction system throughout distinctive stages of the embryogenesis, particularly in the sinoatrial and

FIGURE 2 **12-Lead Resting ECG and Ambulatory ECG Monitoring (Patient 1)**



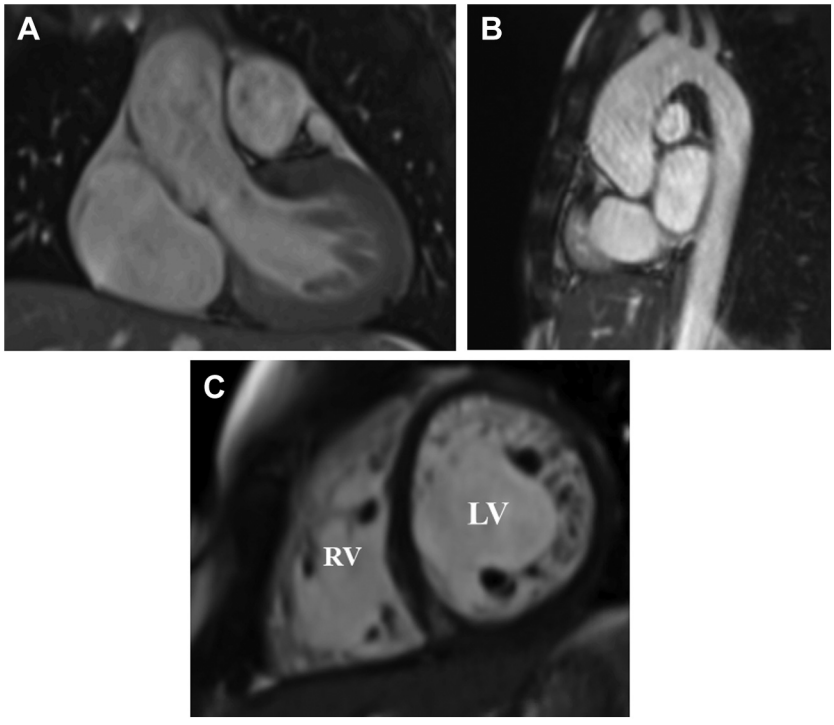
(A) 12-lead resting ECG: sinus bradycardia (40 beats/minute) and isolated ventricular ectopic. **(B)** Ambulatory ECG monitoring: sinus pauses (10.5s [B1], 6.5s [B2]), ventricular couplet (B3) and ventricular triplet (B4). ECG = electrocardiogram.

FIGURE 3 **Echocardiographic Images (Patient 1)**



Apical 4-chamber view **(A)** and short axis view **(B)** showing noncompaction cardiomyopathy. **(C and D)** Long-axis view showing aortic root dilatation **(C)** and ascending aortic dilatation **(D)**.

FIGURE 4 **Cardiac Magnetic Resonance Imaging (Patient 1)**



Oblique coronal view **(A)** and oblique sagittal view **(B)** demonstrating mild aortic root dilatation (maximum systolic diameter at the level of sinus of Valsalva of 35 mm in systole and 30 mm at the level of the sinotubular junction [Z-score +3.9 and +4.2, respectively, Kaiser dataset]) and moderate ascending aortic dilatation (maximum systolic diameter of 38 and 35 x 36 mm in diastole [Z-score +6.7, Kaiser dataset]). **(C)** End-diastolic short-axis view showing biventricular noncompaction.

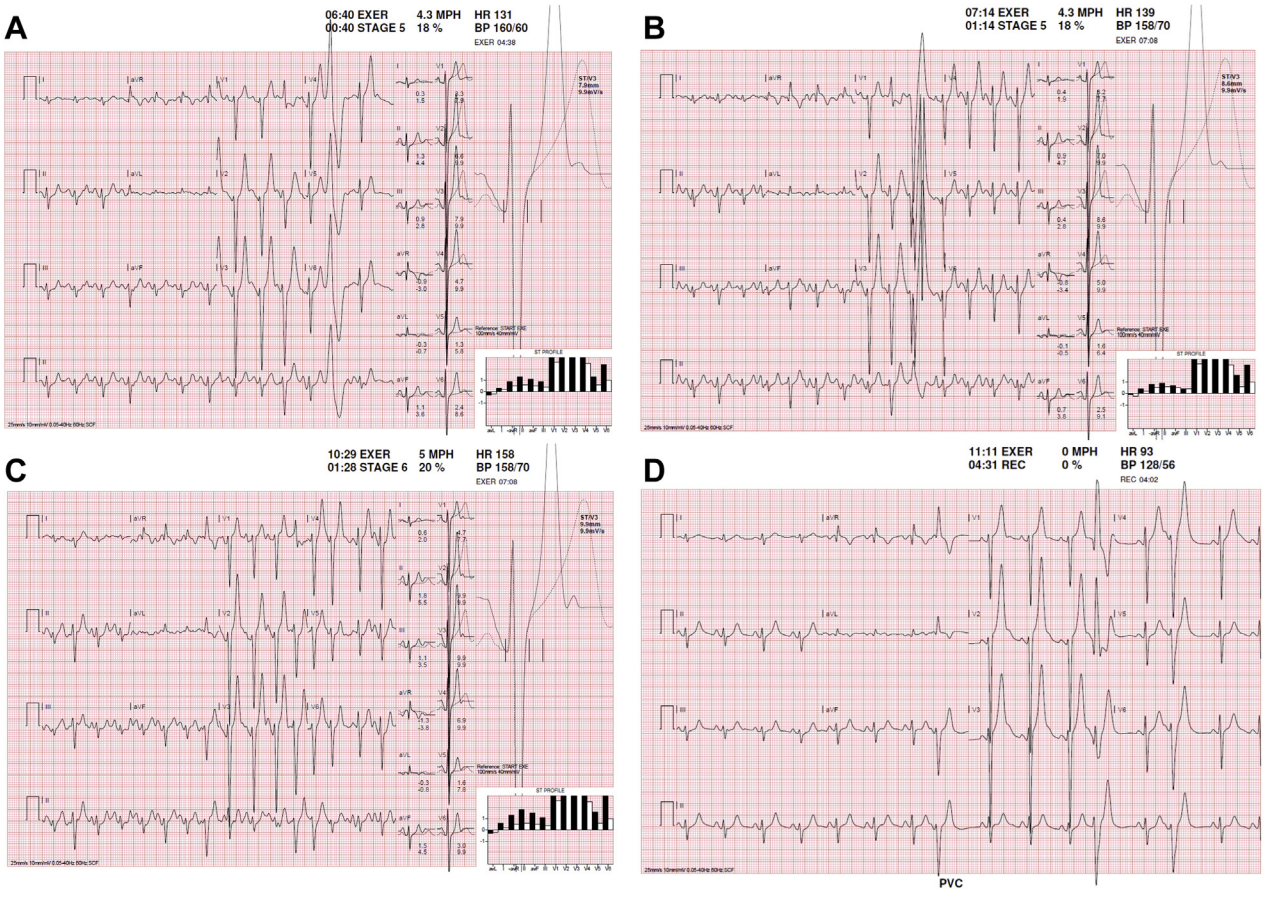
atrioventricular node.[6] Precisely, it generates the hyperpolarization-activated "funny" (I_f) currents that are responsible and modulate the pacemaker activity in the sinoatrial node.[1,2] Hence, as a result of the I_f channel malfunction, mutations in the *HCN4* gene had been primarily associated with sinus bradycardia and sick sinus syndrome and, more recently, with a wide spectrum of phenotypes including a few cases of *HCN4* mutations linked with NCC and aortic dilatation.[2-5,7,8]

The pathogenic variant p.Gly482Arg on *HCN4* gene was first reported by Milano et al (2014),[1] associated with sinus node dysfunction and NCC (**Table 1** [Family B]). In the same issue, Schweizer et al[3] reported a family in which this variant segregated with the same phenotype (sinus bradycardia and NCC) throughout 4 generations (**Table 1** [Family C]).

In 2015, Millat et al[5] reported the first cases of aortic dilatation in 3 French sisters (**Table 1** [Family D]) affected with this variant who also presented sinus bradycardia and NCC. In our study,[3] in line with the aforementioned publications, all family members presented sinus bradycardia. In addition, our proband developed sick sinus syndrome, also concurring with previous reports.[5] Moreover, all 3 of them had NCC and mild LV dilatation with no severe systolic dysfunction. This could reflect a phenotype with LVNCC associated to LV dilatation as previously reported[9] or a more physiological compensatory mechanism in the presence of significant bradycardia.

Furthermore, in 2016, Vermeer et al[4] reported 8 families with *HCN4* mutations, bradycardia, NCC, and aortic dilatation. Precisely, 20 of 26 patients (77%) and 6/9 (66.6%) patients with the p.Gly482Arg variant had aortic dilatation (**Table 1** [Family E]) with age-dependent penetrance. Similarly, we observed significant aortic dilatation in the proband and borderline aortic dilatation in his sister, but we could not demonstrate the age-dependent penetrance of the aortic dilatation as it was already present in the younger members of this family and absent in the mother.[4] In addition, in 2019, Hanania et al[7] described

FIGURE 5 Exercise Test (Patient 1)



(A) Isolated ventricular ectopics during exercise. **(B)** Bidirectional couplet during exercise. **(C)** Maximum heart rate (158 beats/min) at peak exercise. **(D)** Isolated ventricular ectopics during recovery.

a family with p.Gly482Arg variant and thoracic aortic disease, bradycardia, and NCC (**Table 1** [Family F]).

HCN4 mutations had also been described with defects of the mitral valve, early-onset fibrillation, atrioventricular block, and idiopathic ventricular tachycardia.[1,2,4,8] Moreover, arrhythmias, heart failure, and sudden cardiac death have been reported in NCC.[10] For these reasons, and in view of the young age of our proband, potential for bradycardic arrest, ventricular triplets, and perceived potential risk for malignant arrhythmia, an ICD was inserted for primary prevention. Medical treatment with beta blockers and ARBs was started, as indicated by his presenting features.

Although the association of *HCN4* mutations with bradycardia concurs with the role of *HCN4* channel in cardiac pacemaker, the exact mechanism of NCC, mitral valve defects, and aortic dilatation remains uncertain.[1,3,8] Regarding the latter phenotype, it has been demonstrated that *HCN4* is also expressed in the endothelium of the aorta in mice, data that could potentially explain the development of aortic dilatation in patients with *HCN4* mutations.[4,6]

CONCLUSIONS

Our findings highlight the importance of suspecting *HCN4* gene mutations when sick sinus syndrome, NCC, and aortic dilatation are encountered in clinical practice, particularly with the pathogenic variant p.Gly482Arg. Future studies including larger cohorts are required not only to define more accurate risk stratification and long-term monitoring regarding arrhythmic burden, progression of aortic disease and thresholds for elective surgery, and progression of cardiac muscle disease but also to elucidate the link

between *HCN4* gene mutations, cardiac muscle disease, and aortic dilatation.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work is supported by the NIHR GOSH Biomedical Research Centre. Dr Kaski is supported by the British Heart Foundation, Medical Research Council Clinical Academic Partnership (CARP) award, Max's Foundation, Action Medical Research/LifeArc, and the Great Ormond Street Hospital Children's Charity. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Milano A, Vermeer AMC, Lodder EM, et al. HCN4 mutations in multiple families with bradycardia and left ventricular noncompaction cardiomyopathy. *J Am Coll Cardiol*. 2014;64:745–756.

2. Servatius H, Porro A, Pless SA, et al. Phenotypic spectrum of HCN4 mutations. *Circ Genomic Precis Med*. 2018;11:1–6.

3. Schweizer PA, Schröter J, Greiner S, et al. The symptom complex of familial sinus node dysfunction and myocardial noncompaction is associated with mutations in the HCN4 channel. *J Am Coll Cardiol*. 2014;64:757–767.

4. Vermeer AMC, Lodder EM, Thomas D, et al. Dilation of the aorta ascendens forms part of the clinical spectrum of HCN4 mutations. *J Am Coll Cardiol*. 2016;67:2313–2315.

5. Millat G, Janin A, de Tauriac O, Roux A, Dauphin C. HCN4 mutation as a molecular explanation on patients with bradycardia and noncompaction cardiomyopathy. *Eur J Med Genet*. 2015;58:439–442.

6. Liang X, Wang G, Lin L, et al. HCN4 dynamically marks the first heart field and conduction system precursors. *Circ Res*. 2013;113:399–407.

7. Hanania HL, Regalado ES, Guo DC, et al. Do HCN4 variants predispose to thoracic aortic aneurysms and dissections? *Circ Genomic Precis Med*. 2019;12:573–574.

8. Towbin JA. Ion channel dysfunction associated with arrhythmia, ventricular noncompaction, and mitral valve prolapse. *J Am Coll Cardiol*. 2014;64:768–771.

9. Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. *Lancet*. 2015;386:813–825.

10. Dong X, Fan P, Tian T, et al. Recent advancements in the molecular genetics of left ventricular noncompaction cardiomyopathy. *Clin Chim Acta*. 2017;465:40–44.

KEY WORDS aortic dilatation, cardiomyopathy, HCN4, noncompaction, sinus bradycardia, sinus node dysfunction

APPENDIX For supplemental videos, please see the online version of this paper.