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CASE REPORT

ADVANCED

CLINICAL CASE

Missense Variant E1295K of Sodium Channel SCN5A Associated With Recurrent Ventricular Fibrillation and Myocardial Inflammation

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ABSTRACT

SCN5A was considered an exclusively cardiac expressed ion channel but discovered to also act as a novel innate immune sensor. We report on a young SCN5A variant carrier with recurrent ventricular fibrillation and massive myocardial inflammation whose peculiar clinical course is highly suggestive of such a dual role of SCN5A. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2022;4:280–286) © 2022 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/).

HISTORY OF PRESENTATION: HOW THE PATIENT WAS ADMITTED, PHYSICAL EXAMINATION

A 43-year-old female physician, without any history of previous cardiac or other disease, mother of 2 children, underwent out-of-hospital resuscitation caused by ventricular fibrillation.

PAST MEDICAL HISTORY. Family history regarding sudden cardiac death or other cardiovascular diseases was negative, there was no history of recent infectious disease in the patient or contact persons, and no previous medication or substance abuse.

DIFFERENTIAL DIAGNOSIS. Electrocardiogram (ECG) demonstrated no signs of ion channel disorder or other anomalies. Angiography excluded coronary

LEARNING OBJECTIVES

- To recognize high-risk patients with myocardial dysfunction or arrhythmias of unknown origin at early disease stages and to prioritize them for extended differential diagnostic work-up.
- To translate the feasibility of large-scale state-of-the-art variant screening of cardiomyopathy-associated genes into personalized patient management, which may also include tailor-made therapeutic approaches.
- To employ multimodal diagnostics to facilitate recognition of hidden disease components with therapeutic impact, such as inflammation, which may inflame life-threatening arrhythmias in patients with genetic predispositions.

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artery disease (CAD), while suggesting Takotsubo cardiomyopathy (**Figure 1**). Echocardiography showed rapid resolution of contractile dysfunction compatible with Takotsubo disease (Supplemental Refs. 1,2).

INVESTIGATIONS

Magnetic resonance imaging (MRI) detected dilation of the left ventricle (LV) (184 mL) and of the right ventricle (RV) (183 mL), left ventricular ejection fraction (LVEF) 61%, and left ventricular mass indexed (LVMi) 74 g/m^2, no signs of storage disease or inflammation, and fludeoxyglucose F-18 positron-emission tomography-computed tomography (F^{18}-FDG PET-CT) identified no intramyocardial or other inflammatory foci. Endomyocardial biopsy (EMB) was not conducted at this time.

MANAGEMENT

An implantable cardioverter defibrillator (ICD) was inserted. Bisoprolol 2 x 5 mg per day was initiated, and, herewith, the patient felt healthy and physically able to work under pressure as a physician and mother of 2 young children.

DISCUSSION

At first presentation, this patient was diagnosed and treated according to current guidelines (Supplemental Refs. 3-8).

FOLLOW-UP. Unfortunately, 16 months later she was readmitted upon multiple ICD shock deliveries for recurrent ventricular fibrillation (VF). This time, EMB was immediately conducted, revealing massive myocardial inflammation (**Figure 2A** [first biopsy]) without evidence of giant cell or eosinophilic myocarditis or myocardial sarcoidosis (Supplemental Ref. 9). Results of a reverse transcriptase-polymerase chain reaction (RT-PCR) test was negative for multiple DNA/RNA viruses (Supplemental Refs. 10,11).[1]

Variant screening of 255 cardiomyopathy-associated genes identified heterozygosity for a novel likely pathogenic E1295K variant of SCN5A (**Figure 2B**) in a highly conserved functionally critical domain (Supplemental Files 1 and 2, Supplemental Refs. 12-15).[2] With the physician patient we discussed the combination of a pro-arrhythmogenic gene variant with myocardial inflammation, a situation for which no established guideline is available. A joint decision was made to initiate an immunosuppressive treatment course, with the rationale to reduce local inflammation as a possibly treatable trigger of her still-uncontrolled arrhythmias. Subsequently, arrhythmia load declined, and no more ventricular tachycardias (VTs) occurred. In EMBs after prednisolone therapy (**Figure 2A** [second biopsy]) intramyocardial inflammation had vanished. However, anomalies of circulating immune cells (PBMCs) persisted over >4 years (eg, high interleukin (IL)-2 release).

Figure 2C summarizes the patient's course during her first presentation (left), immunosuppressive therapy (middle), and another year later at third presentation (right) when VF occurred again within the context of flu-like symptoms and massive mental stress. Regarding anti-arrhythmic measures beyond dual chamber ICD and beta-blocker therapy, flecainide—as potent sodium channel inhibitor—was added this time (Supplemental Ref. 16) and emerged highly efficient in further reducing her arrhythmia load.

CONCLUSIONS

Anomalous immune activation[1] (Supplemental Refs. 10,11,17-21) and macrophages (Supplemental Refs. 22,23) are involved in multiple types of cardiomyopathies but, so far, are not considered in the context of ion-channel cardiomyopathies. SCN5A encodes the ion-conducting α-subunit of the cardiac sodium channel (Nav1.5) responsible for initiation and propagation of action potentials and thereby determining cardiac excitability and conduction of electrical stimuli through the heart. SCN5A variants are associated with a clinical spectrum ranging from long QT and Brugada syndrome to dilated cardiomyopathy (DCM). SCN5A was considered an exclusively cardiac ion channel. Recently, however, it was discovered that a SCN5A splice variant is also expressed in macrophages, where it activates innate immune signaling for antiviral defense (Supplemental Refs. 24-28).[3,4] Pioneering work found

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
CMP = cardiomyopathy
DCM = dilated cardiomyopathy
EMB = endomyocardial biopsy
LV = left ventricle
LVEF = left ventricular ejection fraction
LVMi = left ventricular mass index
MRI = magnetic resonance imaging
PBMC = peripheral blood mononuclear cells
PCR = polymerase chain reaction
RT-PCR = reverse transcriptase polymerase chain reaction
SCD = sudden cardiac death
SCN5A = sodium voltage-gated channel alpha subunit 5
VES = ventricular extrasystole
VF = ventricular fibrillation
VT = ventricular tachycardia

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.

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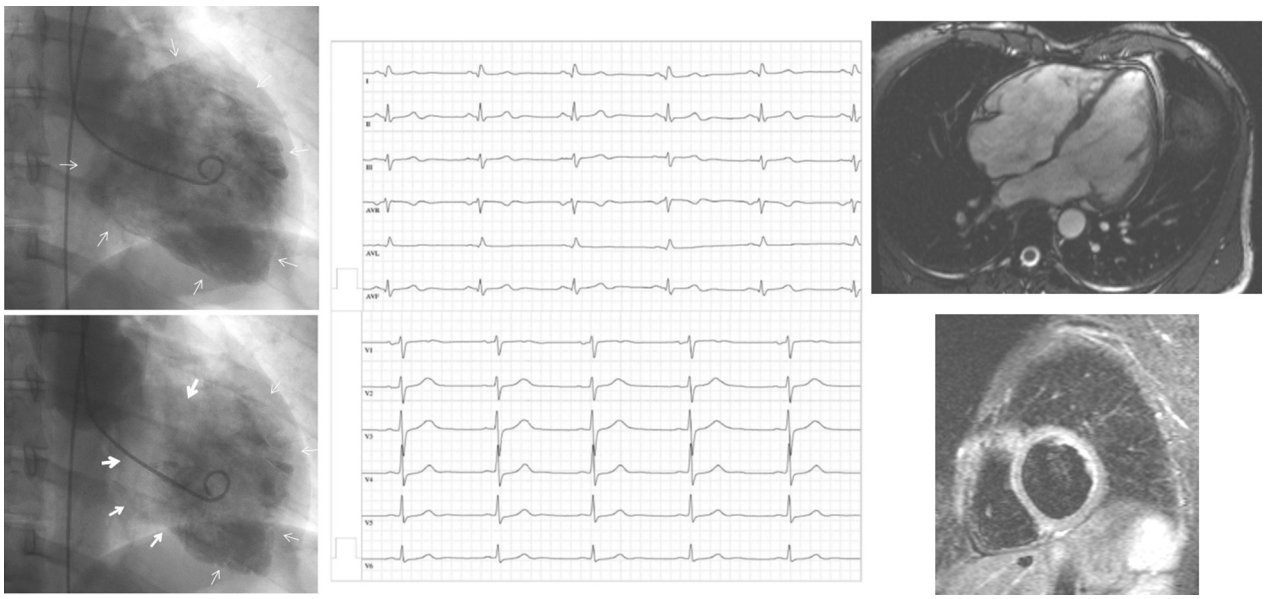
FIGURE 1 Findings at Initial Presentation



A 43-year-old female physician, without history of previous cardiac or other disease, underwent out-of-hospital resuscitation for ventricular fibrillation. The electrocardiogram was inconspicuous, and angiography excluded coronary artery disease, while suggesting Takotsubo disease. Magnetic resonance imaging and fludeoxyglucose F-18 positron-emission tomography-computed tomography (F^{18}-FDG PET-CT) identified no intramyocardial or other inflammatory foci or storage disease. An endomyocardial biopsy was not conducted at this time (compare with **Figure 2**).

that SCN5A modulates the phagocytic pathway of myelin degradation in macrophages in multiple sclerosis (MS) and that expression of the human macrophage variant of SCN5A in mice protects them against experimental autoimmune encephalomyelitis (MS model) (Supplemental Refs. 27,28).[4] Endosome-associated variants of SCN5A thus act as novel innate immune sensors, suggesting that patients so far classified as "pure" myocardial ion-channel disease cases may carry independent "immunologic" risk through hitherto-neglected anomalous function of their mutant ion channels (**Figure 3**).

From a clinical perspective, there are multiple obstacles to unequivocal detection of myocardial inflammation as a precipitating factor for life-threatening arrhythmias. Even in narrowly focused patient cohorts for whom genetic predisposition is suspected—such as by detection of pathogenic variants—this requires significant additional diagnostic work-up (cardiac MRI, EMB, PET-CT), which may not be feasible in all cases. Thus, a large fraction of patients carry ICDs, often preventing reliable cardiac MRI diagnostics, and diagnostic accuracy of EMB may be limited by sampling error (Supplemental Ref. 10).[1,5] Postmortem examination cannot possibly detect transient bouts of inflammation during the often prolonged diseases course, and unless inflammation persists until the time of death there will be—at most—unspecific residues of past inflammation. These, however, for example: interstitial fibrosis or dilation of the myocardium, can no longer be distinguished from DCM resulting from other mechanisms. It is highly likely that only a small fraction of all inflammation-triggered arrhythmic events will be clinically detected, generating a blind spot regarding the potential use of anti-inflammatory treatments in this context. Indeed, recognition of our patient's myocardial inflammation was a serendipitous result of sequential EMBs "enforced" by her refractory life-threatening arrhythmias. Notably, anti-arrhythmic potential of immunosuppression does not rely on genetic SCN5A variants because inflammation per se may cause dysfunction of normal SCN5A channels.

Haas et al[2] (Supplemental Ref. 12) generated a genetic atlas of human DCM. Although the specific variant detected in our case was not seen in that study, SCN5A variants were among the most commonly mutated genes (**Figure 2C**), and overlap between DCM- and channelopathy-associated variants was high. One possible explanation for occurrence of

FIGURE 2 **Extended Diagnostics and Clinical Course**

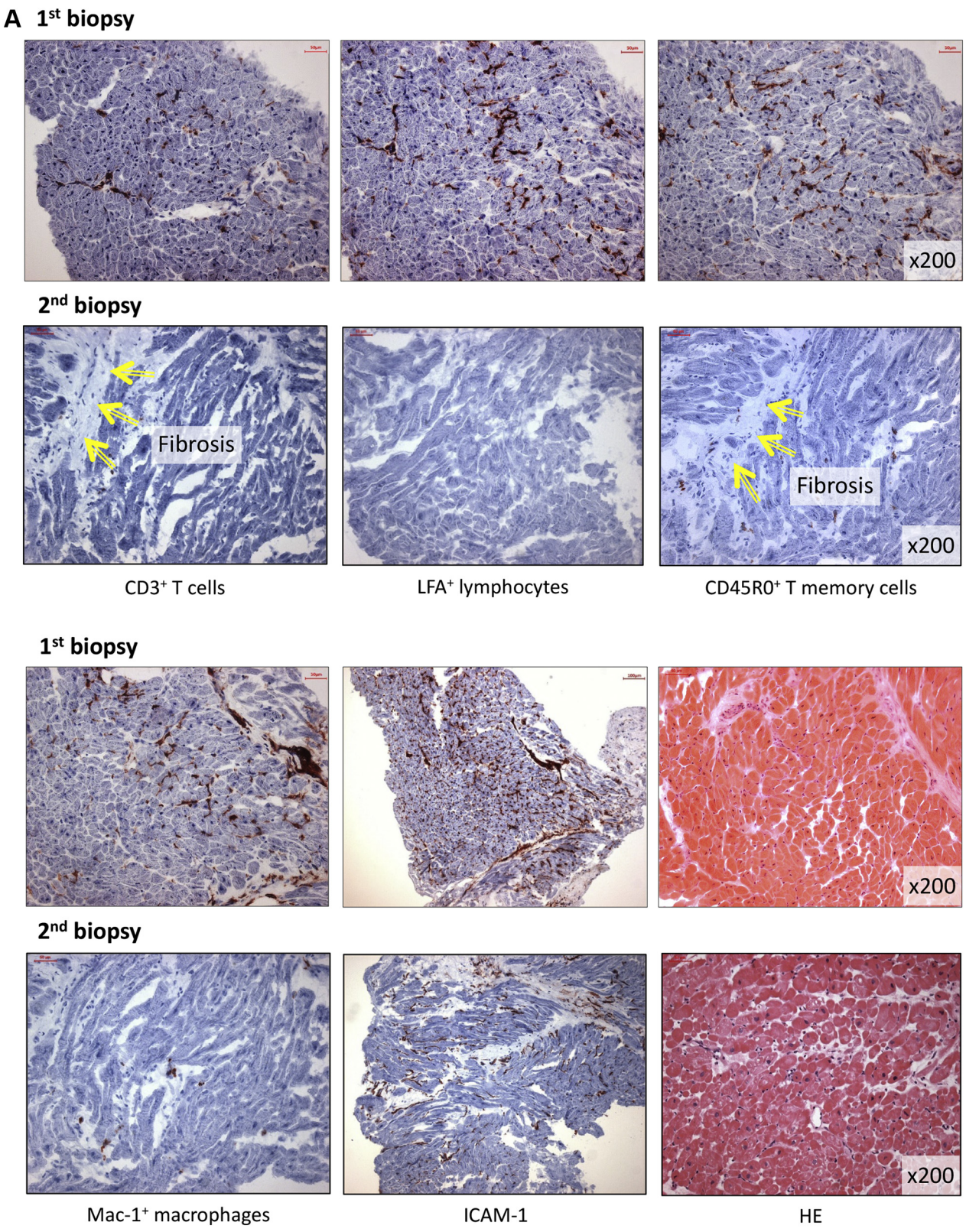


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FIGURE 2 Continued

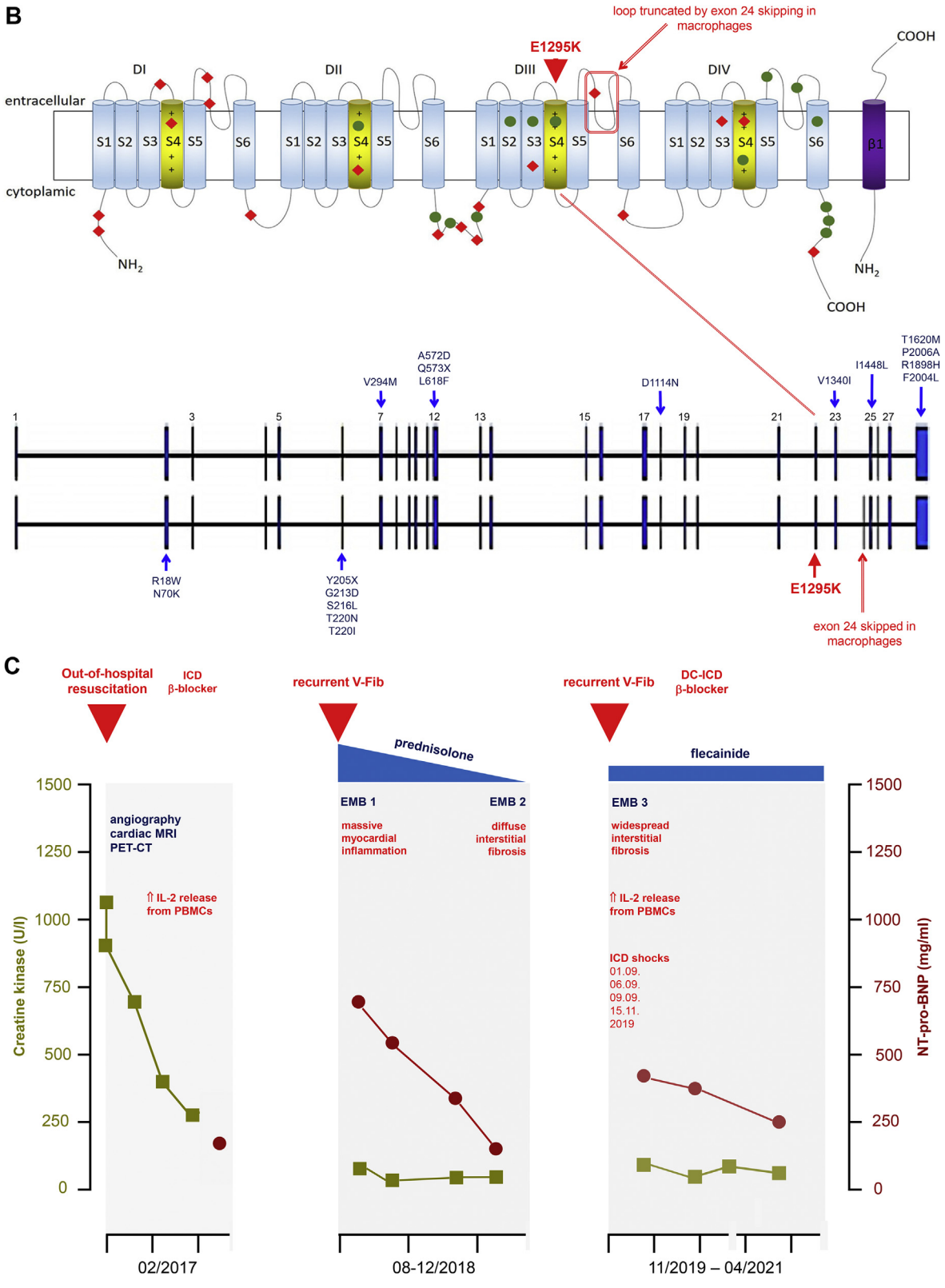
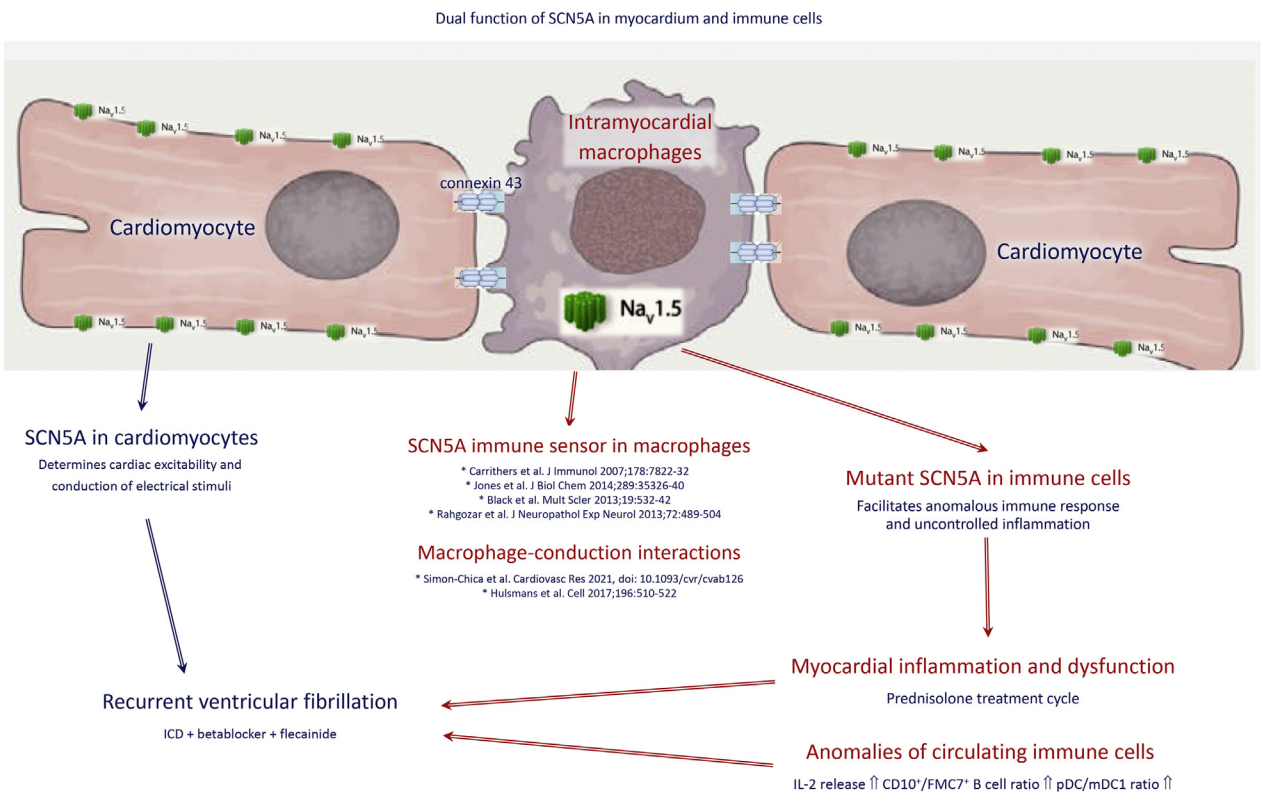


FIGURE 3 Model of a Dual Role of SCN5A in Heart and Immune System



Several recent basic research and clinical investigations, including the current case, are consistent with—and suggestive of—a dual role of SCN5A, with its well-known functions in the heart plus a hitherto-neglected role as an innate immune sensor imposing independent "immunologic " risk upon variant carriers.

SCN5A variants not only in patients with long QT syndrome or Brugada syndrome but also with DCM would be insidiously progressive myocardial injury enabled by defective function of a mutant SCN5A immune sensor. As malignant arrhythmias are naturally the center of attention in these patients, background deterioration of myocardial structure may go unnoticed over a long time but ultimately yield

FIGURE 2 Continued

(A) Upon re-admission with multiple adequate implantable cardioverter-defibrillator shock deliveries, immediate endomyocardial biopsy (EMB) (= 1st biopsy) revealed massive inflammation (CD3$^+$ T cells: 91/mm^2, CD45RO memory cells: 207/mm^2, Mac-1$^+$ macrophages: 237/mm^2) without evidence of giant cell or eosinophilic myocarditis, or sarcoidosis.[1] Polymerase chain reaction (PCR)/reverse transcriptase polymerase chain reaction (RT-PCR) was negative for multiple DNA/RNA viruses. **(B)** The patient's variant is located immediately before the sequence encoding the S4 transmembrane strand of protein domain III. E1295K is thus in proximity to the downstream extracellular loop encoded by exon 24 which is skipped in macrophages. Other SCN5A variants identified previously[2] are shown in **blue**. All of these are located outside of the loop skipped in macrophages. **C** summarizes the patient's course during 1st presentation **(left)**, through a 3-month prednisolone course **(middle)**, and another year later at her 3rd presentation **(right)** when recurrent ventricular fibrillation (V-Fib) occurred again within the context of flu-like symptoms and massive mental stress. Regarding anti-arrhythmic measures beyond dual-chamber implantable cardioverter-defibrillator (DC-ICD) and beta-blocker, flecainide as potent sodium channel inhibitor was added this time and emerged highly efficient in further reducing her arrhythmia load. In EMBs after immunosuppression (= 2nd biopsy) inflammation had vanished and interstitial fibrosis suggested healing. Circulating immune cell anomalies persisted for >4 years, including high interleukin (IL)-2 release. MRI = magnetic resonance imaging; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; PBMC = peripheral blood mononuclear cell; PET-CT = positron emission tomography-computed tomography.

patients with DCM and SCN5A variants. Without extensive diagnostic work-up of variant carriers, it must remain unknown whether these patients' phenotype is an unspecific residuum of past inflammation or a result of other pathomechanisms. In any case, their observed DCM association cannot be explained by arrhythmogenic impact of the SCN5A variants alone. In view of possible therapeutic relevance, it appears recommendable to further evaluate the hypothesis of independent immunologic risk in major SCN5A variant-carrier cohorts.

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KEY WORDS inflammation, innate immune response, ion channel diseases, ion channel functions, variant screening

APPENDIX For supplemental material and references, please see the online version of this article.