Supplemental File S1

regarding the manuscript *"Missense variant E1295K of sodium channel SCN5A associated with recurrent ventricular fibrillation and myocardial inflammation"*

The following pages provide full details of the next generation sequencing-based variant screening of 255 cardiomyopathy-associated genes as well as references and bioinformatics studies relevant to the Case Report.

1. Electrophysiological cell biological data obtained in non-immune cells by Abriel et al. 2001. With regard to the only recently discovered function of SCN5A acting as a novel innate immune sensor in macrophages, key subject of the Case Report, no cellular level studies have been published.

2. *In silico* phylogenetic conservation analysis of SCN5A variant E1295K, based on 40 orthologous sequences from different species with 70-100% homology, which shows that Glu(E)1295 is a highly conserved residue.

3. Variant effect predictor software output and SCN5A paralogue analyses which provide adjunctive data regarding E1295K variant effects.

4. References regarding the specific SCN5A variant E1295K.

5. References regarding the same Glu(E)>Lys(K) amino acid substitution, however in other regions of the SCN5A protein.

6. E1295K is located in a highly conserved functionally critical domain in transmembrane segments S3 and S4 of the domain III region (compare Fig. 2B).

7. The class of pathogenicity for E1295K according to the ACMG2015 criteria (Richards *et al.* Genet. Med. 2015;17:405-24) is "likely pathogenic".

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DETAILED RESULTS

Gene: SCN5A (Encoding the protein: Sodium channel protein type 5 subunit alpha) NP_932173.1:p.Glu1295Lys/NC_000003.11:g.38603986C>T

Heterozygous carrier: Variant occurs in only one copy of the gene.

Next Generation Sequencing statistics: Depth of coverage: 211. Quality of the variant (0-255): 255.

Variant nomenclature: Nucleotide code: NM_198056.2:c.3883G>A, NC_000003.11:g.38603986C>T. Amino acid code: NP_932173.1:p.Glu1295Lys. dbSNP ID: rs199473218. Alternative names at the protein level: Glu1295Lys, E1294K isofB, NP_932173.1:p.E1295K. Located in: exon 22.

Pathogenicity: likely to be pathogenic or disease-causing (+?).

Population frequency: mutation (not found in controls).

Number of articles/communications that mention it: 14. Number of described families: 2. Number of families with additional unpublished information: 1.

Clinical information

- Previously described: This variant has been previously reported in association with long QT syndrome (Abriel et al., 2001, see below).

We have previously identified this variant in a 29-year-old female patient with suspicion of recurrent myocarditis, who had shown unspecified alterations on ECG before the myocarditis episodes. Her sister had hypertrophic cardiomyopathy but no history of myocarditis or arrhythmic events. She also carried this SCN5A variant along with a missense variant of unknown clinical significance in FLNC.

- Reported in public databases: It is included in dbSNP (rs199473218). ClinVar classifies it as of uncertain significance and pathogenic according to three independent submitters. It is not reported in public databases of the general population (1000 Genomes Project, Exome Variant Server, ExAC, or TOPMed). Two paralogue variants associated with disease have been reported: p.Glu1308Asp in SCN1A and p.Asp1338Tyr in CACNA1A, associated with febrile seizures and cerebellar ataxia, respectively.

- Information on the variant and other similar variants: In a study by Abriel et al. from 2001, the p.Glu1295Lys mutation in the SCN5A gene was reported in an 18-year-old male individual diagnosed with long QT syndrome type 3 (QT of 480 msec on ECG, without symptoms) and was not detected in 600 control chromosomes.

This variant is located in transmembrane segments S3 and S4 of the domain III region. These regions are of high functional importance. In domain III (amino acids 1187-1501), we have only identified one variant causing the same amino acid change as the variant identified in this study. p.Glu1225Lys has been identified in at least fourteen patients (from 12 different pedigrees) with Brugada syndrome. There are some reports (4) of sudden death in relatives without genetic testing in these families. Additionally, two other variants introducing a lysine (Lys) have been reported in the same domain. p.Asn1380Lys has been identified in four patients (from 3 families) with Brugada syndrome. One carrier suffered sudden death. p.Asn1474Lys has been identified in two DCM patients and in one with long QT syndrome.

Taking into consideration all SCN5A transmembrane domains, six other variants with the same amino acid change are recorder in our database: p.Glu161Lys, p.Glu375Lys, p.Glu901Lys, p.Glu1548Lys, p.Glu1574Lys, and p.Glu1784Lys. These variants have been identified in several patients with Brugada syndrome and long QT syndrome. Among them, only p.Glu161Lys and p.Glu1548Lys were identified in the general population, respectively in one and two individuals in the gnomAD database. *See table: Report of multiple variants with the same amino acid change (Glu>Lys), in the appendix 1.*

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Functional study / Animal model

Abriel et al. studied the functional consequences of this variant by expressing it in HEK293 cells. The results showed that this variant alters the gating process. This mutation shifts the voltage window of cardiac Na channels to more positive ones where rectifier potassium currents are less effective; it promotes sustained channel activity only over a very narrow window of voltages, ones that differ from the WT in the voltage range of the window. This shift provokes a prolongation of the action potential duration.

Bioinformatics study

The Glu1295 residue is located in the extracellular domain (residues 1292-1295) between transmembrane segments S3 and S4 of repeat domain III of the sodium channel protein type 5 subunit alpha, adjacent to the voltage sensor segment (S4, amino acids 1296-1317). As we discussed above, an experimental assay performed on this variant showed significant changes in sodium channel activity. Our *in silico* phylogenetic conservation analysis, based on 40 orthologous sequences from different species with 70-100% homology (up to western clawed frog), shows that Glu1295 is a highly conserved residue. Thirty-nine of the aligned sequences had a residue at this position, which was glutamic acid in all of the analyzed cases. Moreover, comparison with paralogous sequences for SCN5A showed that this residue is also highly conserved in them, and two paralogue variants have been mapped to this residue: p.Glu1308Asp in SCN1A and p.Asp1338Tyr in CACNA1A, associated with febrile seizures and cerebellar ataxia, respectively. This variant causes a change from an amino acid with an acidic side chain (glutamic acid, Glu) (GAG) to another amino acid with a basic side chain (lysine, Lys) (AAG). There are small differences in physicochemical properties (polarity, charge, and volume) between glutamic acid and lysine (Grantham distance: 56 [0-215]).

Variant effect predictors

(These predictors have limited clinical utility and should be used only as supporting evidence)

Predictor	Prediction	Score	Version
MutationTaster	Disease-causing	1	access date: 20 Apr 2018
DANN		0.999057	July, 2015
FATHMM MKL Coding		0.96215	July, 2015
FATHMM MKL Non-Coding		0.99095	July, 2015

MutationTaster: ranges from 0 to 1. Values close to 1 indicate a high degree of prediction accuracy. DANN: the higher score the more potential pathogenicity. Values between 0 and 1. FATHMM: The higher score the more potential pathogenicity. Coding and non-coding variants are scored independently. Values between 0 and 1.

Primary functions of the protein

This gene encodes the tetrodotoxin-resistant voltage-gated sodium channel known as Nav1.5, which is predominantly expressed in the heart. Sodium channels are composed of an alpha subunit, such as Nav1.5, that interacts with another auxiliary beta subunit. This protein is responsible for the rapid sodium current that produces the membrane potential during phase 0 of the cardiac action potential. Thus, the function of Nav1.5 is essential for the generation and transmission of impulses in excitable tissues.

Related phenotypes and inheritance patterns

To date, loss-of-function mutations in the SCN5A gene have been associated with Brugada syndrome (BrS) (Chen et al., 1998; Bezzina et al., 1999; Remme et al., 2006), progressive cardiac conduction disease (Lev-Lenègre disease) (Schott et al., 1999; Tan et al., 2001), dilated cardiomyopathy (DCM) (McNair et al., 2004; Olson et al., 2005; Laurent et al., 2012; Bezzina et al., 2003), sick sinus syndrome (SSS) (Benson et al., 2003; Smits et al., 2005), and atrial fibrillation (AF) (Makiyama et al., 2008).

On the other hand, gain-of-function mutations in this gene cause long QT syndrome (LQTS) type 3 (Wang et al., 1995; Remme et al., 2006) and have also been recently involved in multifocal ectopic Purkinje-related premature contractions (MEPPC). Some of these mutations are also associated with AF and DCM.

Recently, Riele et al. (2017) associated SCN5A mutations with non-canonical mechanisms for disease pathogenesis and suggested that there is an interaction between the desmosome and the sodium channel encoded by the SCN5A gene. They speculated that Nav1.5 not only forms ion-selective pores but is also a functional protein in a functional adhesion/excitability complex with mechanical junctions. This could lead to different phenotypes: predominantly structural (e.g., dilated cardiomyopathy), predominantly electrical (e.g., Brugada syndrome, long QT syndrome), or a mixed electrical and structural phenotype (e.g., arrhythmogenic right ventricular dysplasia/cardiomyopathy). As such, the affected protein interaction, more than the exact gene mutation, may determine the phenotype. Most commonly, pathogenic SCN5A mutations show an autosomal dominant inheritance pattern with incomplete penetrance, but recessive forms with homozygous or compound heterozygous mutations have also been described.

Conclusions

This variant has previously been described in a single case with long QT syndrome in the literature. In our center, we have also identified it in a woman with history of recurrent myocarditis and previous unspecified alterations on ECG. A functional study of this mutation has shown an alteration on the cardiac sodium current consistent with the development of LQTS. Missense variants causing the same amino acid change (Glu>Lys) have been described as disease-causing in several patients affected with Brugada syndrome or long QT syndrome, and there are isolated reports of carriers with cardiomyopathies. In fact, the SCN5A gene has also been associated with dilated cardiomyopathy with a high burden of arrhythmias/conduction disease; nonetheless, DCM-related variants are clustered in a different region of this variant. Cosegregation study could be useful to better determine its pathogenic role. At this point, this variant cannot be used for predictive testing.

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APPENDIX: SUPPLEMENTARY INFORMATION

Detailed description of the families (variant: p.Glu1295Lys, gene: SCN5A)

Family 3423 [reference: 1]

Country of origin of the family (or of the publication): Unknown. Ethnicity: Western Caucasian.

Variant carriers with available information: 1 (long QT syndrome: 1).

Adverse events reported in the family – no sudden death has been reported; (see tables).

Family 72060 [Unpublished]

Country of origin of the family (or of the publication): United Kingdom.

Variant carriers with available information: 2 (cardiomyopathy, hypertrophic: 1, with unexplained abnormalities: 1).

Adverse events reported in the family – no sudden death has been reported; (see tables).

Other variants in the family: carriers with p.Arg879His (gene FLNC): 2.

- Patient 150052: Incidental recurrent myocarditis.

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Table: Genetic and clinical characteristics of mutant carriers without documented adverse events (variant: p.Glu1295Lys, gene: SCN5A)

Patient ID	Family ID	Variant	Other mut.	Clinical diagnosis	Sex	Age at DX	Age at last FU	QTc (Max)	Atr. fib.	FHSD	VT-VF-EV	Previous syncope	CCD	Triggers	Comment
17019	3423	+	No	Long QT Syndrome	Male	18	18	480	?	-	?	-	-	-	
150052	72060	+	Yes	Recurrent myocarditis + unspecified ECG changes	Female	<28	28	?	?	?	?	?	?	-	
176047	72060	+	Yes	Cardiomyopathy, Hypertrophic	Female	23	23	378	?	?	?	?	-	-	

Variant: + = yes, +(O) = obligate carrier, +(H) = homozygous carrier; QTc (max): maximal corrected QT interval (milliseconds); Atr. fib.: atrial fibrillation ([C] chronic, [P] paroxysmal); FHSD: family history of sudden death; VT-VF-EV: [1] non-sustained ventricular tachycardia, [2] sustained monomorphic ventricular tachycardia, [3] sustained polymorphic ventricular tachycardia, [4] torsade de pointes, [5] ventricular fibrillation, [6] frequent premature ventricular beats; CCD: cardiac conduction disease ([1] sinus node dysfunction or 1st degree AV block, [2] 2nd degree AV block, [3] 3rd degree AV block, [4] left bundle branch block, [5] right bundle branch block, [6] left anterior hemiblock, [7] left posterior hemiblock, [8] pacemaker implanted). Shaded rows represent index cases.

Patient150052: variant p.Arg879His (gene FLNC). **Patient176047:** variant p.Arg879His (gene FLNC).

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Selected references (variant: p.Glu1295Lys, gene: SCN5A)

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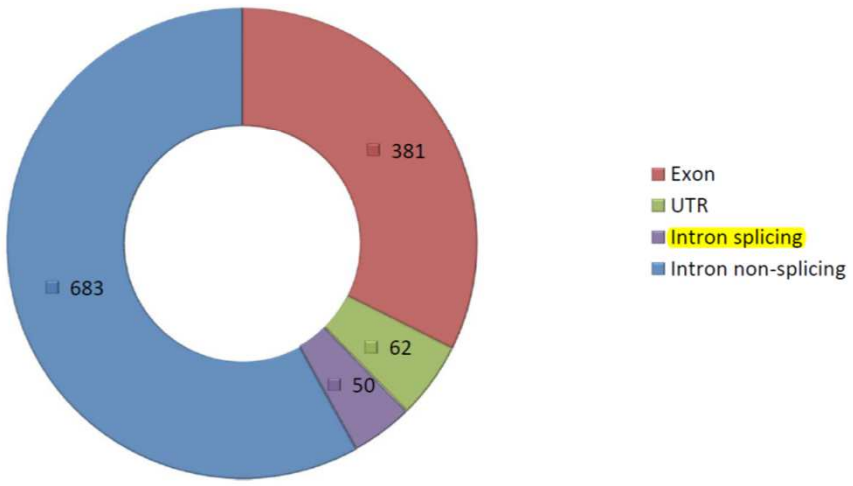
APPENDIX: OTHER IDENTIFIED VARIANTS

AVAILABLE INFORMATION ON OTHER IDENTIFIED VARIANTS

We have identified other genetic variants that we do not consider to be associated with disease development, either because they have been reported in healthy controls or because they do not affect protein structure or function.

Region	Variants found
Exonic	**381**
Synonymous	227
Nonsynonymous	148
Insertion	4
Deletion	2
Intronic	**733**
Intronic splicing	50
UTR	**62**
Total	**1176**



Only high-quality variants are included (QUAL ≥170)

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APPENDIX 1: *Report of multiple variants with the same amino acid change (Glu>Lys).*

Variant	Pathogenicity	Population frequency	Phenotypes (patients)	Families	Affected carriers	Healthy carriers	Events (patients)	References
SCN5A p.Glu161Lys	++	0%	Brugada Syndrome (23) Hereditary bundle branch system defect (8) Long QT Syndrome (1)	13	27	4		38
SCN5A p.Glu375Lys	+?	0%	Brugada Syndrome (2)	1	2	0	Sudden death (1)	0
SCN5A p.Glu901Lys	+?	0%	Brugada Syndrome (6)	4	6	0	Cerebrovascular accident (without death) (1)	9
SCN5A p.Glu1225Lys	+?	0%	Brugada Syndrome (14) Hereditary bundle branch system defect (2) Cardiomyopathy, Dilated (1)	13	15	2	Sudden death (4)	27
SCN5A p.Glu1548Lys	?	0%	Brugada Syndrome (1)	1	1	0	Appropriate ICD discharge (1)	6
SCN5A p.Glu1574Lys	?	0%	Brugada Syndrome (1)	6	1	0		5
SCN5A p.Glu1784Lys	+++	0%	Long QT Syndrome (112) Brugada Syndrome (35) Hereditary bundle branch system defect (14) Short Qt Syndrome (2) Isolated Noncompaction of the Ventricular Myocardium (1) Sudden death(2)	64	133	7	Sudden death (24) Appropriate ICD discharge (4)	110

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p.Glu161Lys

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Patient ID		**DOB**	
Sample / Project	19T01818 / P-201939228	**Date of report**	5 Apr 2019

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