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Absence of a Primary Role for *SCN10A* Mutations in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

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Abstract

Prior reports have identified associations between *SCN10A* and cardiac disorders, such as atrial fibrillation and Brugada syndrome. We evaluated *SCN10A* in 151 probands with ARVD/C. In this cohort, 10 putatively pathogenic *SCN10A* variants were identified, including a novel frameshift insertion. Despite a known role for the encoded protein in peripheral nerve function, the proband with the frameshift variant had no discernible neurological abnormalities. Arrhythmic phenotypes were not different between those with a rare variant in *SCN10A* and those without. The prevalence of rare variants in *SCN10A*was similar among ARVD/C probands with and without a desmosome mutation and similar among healthy Caucasian controls. These results indicate the absence of a primary role for *SCN10A* mutations in *ARVD/C*.

Keywords

SCN10A; Arrhythmogenic right ventricular cardiomyopathy; Sudden cardiac death

SCN10A encodes the alpha subunit of $Na_v1.8$, a voltage-gated sodium channel expressed in nociceptive neurons of dorsal root ganglia and intracardiac neurons. Although the mechanism by which *SCN10A* impacts cardiac electrophysiology remains unknown, associations between *SCN10A* and conduction parameters in genome-wide analyses suggest a functional role. Indeed, rare variants in *SCN10A* have been implicated in Brugada syndrome (1, 2) and atrial fibrillation (3). In addition, cardiac conduction delay is a characteristic feature of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), an inherited cardiomyopathy with prominent arrhythmias. The genetic cause of

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ARVD/C is unknown in approximately 50 % of cases. We sought to identify the prevalence and clinical significance of rare *SCN10A* variants in ARVD/C.

SCN10A was screened using targeted next generation sequencing among 151 unrelated patients (87 [58 %] male, 33.3 ±13.6 years) with definite ARVD/C as per 2010 Task Force Criteria. Half (n=80, 53 %) of subjects harbored an ARVD/C-associated pathogenic desmosomal mutation, and most were Caucasian (n = 146, 97 %; Asian [n = 2], African-American [n=1], Hispanic [n=2]). Potentially pathogenic variants were excluded if they had a minor allele frequency (MAF) >1 % in the Exome Variant Server (release ESP6500SI-V2), 1000-Genomes Project, or Exome Aggregation Consortium or if they were present in dbSNP-131. Variants were included if in silico analyses predicted an effect on protein function by SIFT≤0.05 and Polyphen2≥0.900. Variants were confirmed by Sanger sequencing. All subjects gave written informed consent; the study was approved by the Johns Hopkins Institutional Review Board.

Overall, 10 putatively pathogenic *SCN10A* variants (9 missense, 1 frameshift mutation) were identified in 9 unrelated ARVD/C patients (Table 1), corresponding to an overall yield of 6.0 %(n = 9/151). One individual harbored two missense variants (p.Arg814His and p.Tyr158Asp) in *cis*. Seven (70 %) variants were previously reported in Brugada syndrome and/or atrial fibrillation (1–3) (Table 1).

Assuming a primary role for *SCN10A* in ARVD/C pathogenesis, we hypothesized that the variants would (1) impact nerve function; (2) be associated with ventricular arrhythmias and abnormal conduction intervals; and (3) be overrepresented in genetically unexplained ARVD/C cases compared to those harboring desmosomal mutations.

We first investigated the role of an *SCN10A* variant on nerve function. Since *SCN10A* is only minimally expressed in the myocardium, we assessed peripheral nerve conduction velocity and intra-epidermal nerve fiber density (IENFD), as done previously (4). Because the effect on nerve function is likely strongest for a radical mutation, we focused these analyses on the patient with a frameshift mutation (p.Ile1593fs) in the S4-voltage sensor of Domain IV. Bilateral sural and peroneal motor responses were normal and symmetric in this patient. IENFD and quantitative sensory testing, including heat, pain, and vibration thresholds, were normal.

Second, we compared clinical phenotype between ARVD/C patients with and without an *SCN10A*variant. While carriers of an *SCN10A* variant presented younger than noncarriers (24.5 ± 10.9 vs. 34.4± 13.5 years, p = 0.036), no other differences were found (Supplementary Table 1). Specifically, there was no difference in the prevalence of ventricular and atrial arrhythmias (p = 0.870 and p = 1.000, respectively) or cardiac conduction intervals (PR p = 0.250; QRS p = 0.765; QTc p = 0.876).

Last, we compared the burden of *SCN10A* rare variants in genetically unexplained ARVD/C cases to that observed in ARVD/C subjects with a desmosomal mutation. We observed no significant difference in the prevalence of *SCN10A*variants among ARVD/C patients with and without a desmosomal mutation (n = 4 [5 %] vs. n = 5 [7 %], respectively, p = 0.735).

Based on these three lines of evidence, we conclude that *SCN10A* does not play a primary role in ARVD/C. The burden of rare *SCN10A* variants in our cohort was 6 %, similar to the 2.4–3.5 % observed in healthy Caucasian controls (2). These results challenge the controversial role of *SCN10A* and $Na_V1.8$ in cardiac electrophysiology. Prior studies have suggested three possible pathophysiologic mechanisms: (1) a direct effect on late sodium current in cardiomyocytes; (2) an indirect effect on firing frequency of intracardiac neurons; and (3) a modulatory effect on *SCN5A* transcription. While this study was not designed to address the functional significance of *SCN10A*, detailed neurologic evaluation of our frameshift mutation carrier was normal, and arrhythmic propensity among ARVD/C patients with and without *SCN10A* variants was similar. Of note, nonsense mutations in *SCN10A* have been reported in controls (2), and the majority of *SCN10A* variants in our cohort were previously observed in other arrhythmic diseases (1–3). Future studies should investigate the possible modulatory role of *SCN10A* on arrhythmic propensity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Detailed information of the variants and phenotypes of 9 ARVD/C patients carrying rare *SCN10A* variants

	Variant information								Clinical phenotype by task force criteria (TFC)						
	***SCN10A* nucleotide**	***SCN10A* amino acid**	**Reported ID**	**ExAC MAF[a]**	**EVS MAF[a]**	**Polyphen2**	**SIFT**	**Ref**	**Sex**	**Age**	**Repolabn**	**Depol at**	**in Arrhythmia**	**Struct abn**	**Family history**
1	c.4776_4777insGG	p.Ilel593fs	-	-	-	-	-		F	25.7	Major	Minor	Minor	-	-
2	c.41G > T	p.R14L	rsl41207048	0.1928	0.2153	0.998	0	1–3	F	29.2	Major	Minor	Major	-	Minor
3	c.472 T > G	p.Y158D	-	0.0264	0.0384	0.999	0	3	M	19.9	Major	Major	-	-	Major
	c.2441G > A	p.R814H	rsl39861061	0.0313	0.0538	0.932	0.05	3							
4	c.773G > T	p.S258I	-	0.0008	-	0.992	0		M	50.6	Major	Minor	Minor	Major	Major
5	c.2972C > T	p.P991L	rsl38413438	0.0892	0.1	0.985	0.03		M	21.0	Major	Minor	Minor	Major	Major
6	c.3417G > C	p.W1139C	rsl43744796	0.0107	0.0154	1.0	0	2	M	13.1	Major	Minor	Major	Minor	-
7	c.4568G > A	p.C1523Y	rsl42217269	0.1112	0.1845	1.0	0	2,3	F	24.0	Major	Minor	Minor	-	-
8	c.4984G > A	p.G1662S	rsl51090729	0.1566	0.1307	1.0	0	1,3	M	20.4	Major	Minor	Minor	Major	Major
9	c.5605C > T	p.R1869C	-	0.0807	0.0923	1.0	0	1	M	16.6	Major	-	Minor	Major	Major

	Family history/desmosomal mutation			Cardiac conduction parameters			Clinical course					
	# relatives evaluated	**FH of SCD or ARVD/C**	**Desmosomal variant**	**PR interval (ms)**	**QRS interval (ms)**	**QTc interval (ms)**	**Follow-up duration (years)**	**Treatment**	**Sustained VT/VF**	**AFib or AFlutter**	**Cardiac transplant**	**Death**
1	1	No	-	170	78	427	10.8	ICD, sotalol, ablation	Yes	No	No	No
2	2	Yes[b]	-	148	84	408	7.2	ICD, sotalol, ablation	Yes	No	No	No
3	3	No	*PKP2*: deletion exon 11–12	140	100	438	16.0	ICD, sotalol, ablation	Yes	No	No	No
4	3	Yes	*PKP2*: p.IVS10-1G > C	170	88	412	9.3	ICD, amiodarone, ablation	Yes	Yes	No	No
5	3	Yes[d]	*PKP2*: p.IVS10-1G > C	160	110	419	16.2	ICD	No	No	No	No
6	0	No	-	123	92	405	2.0	ICD	Yes	No	No	No
7	1	No	-	156	100	409	21.5	ICD, flecainide	No	No	No	No

8	1	No	-	170	98	438	7.8	ICD, amiodarone, ablation	Yes	No	No	No
9	2	No	*PKP2:* p.Ser587fs	138	94	444	6.3	ICD	Yes	No	No	No

Abbreviations: *MAF* minor allele frequency, *Repol abn* repolarization abnormality meeting TFC, *Depol abn* depolarization abnormality meeting TFC, *Struct abn* structural cardiac abnormality meeting TFC, *FH* family history, *ARVD/C* arrhythmogenic right ventricular dysplasia/cardiomyopathy, *AFib* atrial fibrillation, *AFlutter* atrial flutter, *ICD* implantable cardioverter-defibrillator, *SCD* sudden cardiac death, *VF* ventricular fibrillation, *VT* ventricular tachycardia

[a] Accessed September 2015

[b] Niece of proband has definite ARVD/C according to TFC and carries the same *SCN10A* variant

[c] Brother experienced SCD at age 30, autopsy revealed atherosclerotic heart disease; no DNA available for testing

[d] Identical twin experienced SCD at 19 years of age, diagnosis of ARVD/C at autopsy; no DNA available for testing