Ryanodine Receptor Mutation in Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: Clinical Implications
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Abstract
This is a case of a 40-year-old otherwise healthy and physically active gentleman noted the onset of palpitations while running upstairs the day of admission to the emergency room. On arrival to the emergency room, his heart rate was noted to be 250 beats-per-minute (bpm) and electrocardiogram (ECG) demonstrated ventricular tachycardia (VT). Synchronized electrical cardioversion was performed to sinus bradycardia. He was stabilized and admitted to the hospital. There was demonstration of right ventricular VT with an inferior axis, T-wave inversions in the precordial lead V1-V3 in the presence of epsilon waves on baseline ECG. In addition, he meets two minor criteria with the presence of right ventricular inferior axis VT and T-wave inversions in the right precordial lead V1-V3 in the presence of complete RBBB. A peculiar finding in this patient is the presence of bidirectional couplet PVCs. Genetic testing revealed mutational variants in the desmolakin, junctophilin, and ryanodine receptor (RYR2) gene of unknown significance. Desmolakin mutations have been described in the ARVC/D population and this particular variant (c.3562T>C) has rarely been detected to our knowledge. Junctophilin mutations have not been described in the literature in the context of genetic cardiomyopathies. This mutation has been demonstrated in 0.1% to 0.2% of person of European descent in the NHLBI exome database. The ryanodine receptors are a class of molecular channels involved in intracellular calcium release in various excitable tissues including the heart. They regulate calcium-induced calcium release from the sarcoplasmic reticulum in the cell and are the major drivers of excitation-contraction coupling in the cardiac myocyte. Calcium release in cardiac ventricular myocytes is associated with increases in inotropy and chronotropy, but also predisposes to ventricular arrhythmias due to enhanced excitation-contraction. In addition, present diabetes, hypertension, and dyslipidemia.

Case Presentation
The patient was treated with medical therapy including beta-blockers for VT. A detailed history and physical exam including family history was unremarkable. There was no evidence of ischemic heart disease by computed tomography contrast coronary angiography and an echocardiogram demonstrated a left-ventricular ejection fraction (LVEF) of 50%. Cardiac magnetic resonance imaging (CMRI) was performed and demonstrated right ventricular regional wall motion abnormalities with dysynchrony and a right ventricular end-diastolic dimension index of greater than 110 ml/m2. In addition, late gadolinium enhancement was demonstrated in the right ventricular myocardium. The constellation of clinical findings and imaging studies were consistent with a diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D). The patient eventually underwent implantation of an implantable cardioverter-defibrillator (ICD) for secondary prevention of sudden cardiac death. The patient did well and was discharged home on hospital day seven to follow-up in clinic for further management and genetic testing.

Ten days after discharge home, the patient had sudden onset palpitations and lightheadedness and experienced a defibrillation shock. Interrogation of the device revealed appropriate ventricular tachyarrhythmia therapy in the ventricular fibrillation (VF) zone for ventricular tachycardia. He otherwise felt well after the event and his beta-blocker was increased after his clinic visit. Four months later, the patient experienced another defibrillation shock after sudden onset palpitations and lightheadedness. Interrogation of his device demonstrated ventricular tachycardia at 240bpm treated with defibrillation by his device.

Genetic testing demonstrated heterozygous mutations in desmolakin, junctophilin, and ryanodine receptor genes classified as variants of unknown significance (Table 1).

Discussion
Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a genetic disorder resulting in a spectrum of clinical presentations ranging from asymptomatic individuals to those with ventricular fibrillation storm, biventricular cardiomyopathy, and sudden cardiac death. The diagnosis of ARVC/D can be difficult when presenting data are inconclusive or other diagnoses are entertained by diagnostic testing. However, in our patient the diagnosis can firmly be made by combining clinical and imaging data. The patient meets two major revised criteria for the diagnosis by MRI findings and the presence of epsilon waves on baseline ECG. In addition, he meets two minor criteria with the presence of right ventricular inferior axis VT and T-wave inversions in the right precordial lead V1-V3 in the presence of complete RBBB. A peculiar finding in this patient is the presence of bidirectional couplet PVCs. Bidirectional ventricular tachycardia has been shown to be associated with the diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT). Genetic testing revealed mutational variants in the desmolakin, junctophilin, and ryanodine receptor (RYR2) gene of unknown significance. Desmolakin mutations have been described in the ARVC/D population and this particular variant (c.3562T>C) has rarely been detected to our knowledge. Junctophilin mutations have not been described in the literature in the context of genetic cardiomyopathies. This mutation has been demonstrated in 0.1% to 0.2% of person of European descent in the NHLBI exome database.

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Keywords: Electrocardiogram (ECG); Beta-blockers; Ventricular Fibrillation (VF); Right Bundle Branch Block (RBBB); Premature Ventricular Contractions (PVC); Left Ventricular Ejection Fraction (LVEF); Implantable Cardioverter Defibrillator (ICD); Arrhythmogenic Right Ventricular Cardiomyopathy/dysplasia (ARVC/D)

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**Figure 1:** Electrocardiograms. A - Ventricular tachycardia consistent with right ventricular outflow tract origin, B - Baseline ECG with T-wave inversion in a RBBB pattern in pre-cordial leads V1-V3.

**Figure 2:** A - Magnification of leads V1-V3 with demonstration of epsilon wave and prolongation of the terminal activation of the QRS complex, B - Bi-directionalcouplet PVCs.
abnormal regulation of RYR2 is seen in patients with heart failure and
missense mutations have been associated with sudden cardiac death.
Mutations in the RYR2 result in excess cytosolic calcium in the setting
of catecholaminergic stimulation and generates repetitive abnormal
excitation of the cardiac myocyte. Repetitive calcium release in the
diastolic period during exercise can trigger delayed after-depolarization
and promote ventricular arrhythmias [5].

RYR2 mutations have classically been associated with CPVT [6].
Ryanodine receptor mutations have rarely been described in the
literature in patients with ARVC/D. In a series of families with
the genetic form of ARVC/D with multiple affected family members, Tiso
et al. describe four missense mutations in the RYR2, two of which are
located in the cytosolic domain of the protein. All four are critical for
the regulation of the calcium channel. The authors suggest that in
these families with an autosomal dominant inheritance pattern, a gain-of-
function mechanism may alter calcium influx during physical activity [7].

The RYR2 mutation found in our patient (R1013Q) has not been
described in registries of ARVC/D patients to our knowledge. In
addition, this particular ryanodine receptor mutation is not located
in the classic “hot spot” regions of the gene for CPVT (Figure 3) and
has only been described in one patient with CPVT in a large registry
and in an unexplained drowning after molecular autopsy in another
series [8,9]. The mutation (c.3038 G >A), which substitutes arginine
for glutamine, is a semi-conservative amino acid substitution and
may impact molecular structure in a highly conserved residue in the
mammalian species. It is located in the cytosolic domain of the protein
and may result in instability of the RYR2 and allow calcium leak into
the cytosol during membrane depolarization with physical activity
(Figure 3).

A variant of unknown significance (VUS), as the name suggests, is a
mutation that has not been proven to contribute to disease pathogenesis
or has not been well described or studied. Attempts have been made
to determine the pathogenicity of VUS mutations including in silico
studies to predict phenotypic outcomes from mutational variants [10].
However, exome analyses have suggested that VUS maybe be over-
represented in the general population and may not be the monogenic
cause of certain cardiac channelopathies leading to clinical disease
states [11] Although this mutation is deemed a “variant of unknown
significance”, this case report of the third mutation described in the
literature may be more evidence that this mutation plays a role in
genetic cardiomyopathies, and may have a clinical impact for novel
treatments and family counseling.

The potential therapeutic implications of identifying this mutation
in the RYR2 can be extrapolated from the data on patients with CPVT.
In a study by Van Der Werf et al. the use of the sodium channel blocker
flecainide was associated with a reduction in ventricular tachycardia
in patients with CPVT [12]. Molecular studies of flecainide have
demonstrated differential effects on the ryanodine receptor however
the exact mechanism of action is controversial. In vitro evidence
suggests that flecainide inhibits the RYR2 during its open state which
in turn reduces calcium flux in the diastolic period [13]. However,
the physiologic effect of flecainide on the RYR2 has been called into
question by Bannister et al. who demonstrated that flecainide had an
indirect, sodium and calcium-dependent effect on the RYR2 rather
than direct inhibition [14]. Overall, there may be multiple effects of
flecainide on the RYR2 [15]. There is sparse data on the use of flecainide
in ARVC/D patients.

### Conclusion

Previous studies included the use of class I antiarrhythmic drugs
with reported rare benefit as compared with class III agents [16].
Ermakov et al. studied a small select population of ARVC/D patient
refractory to single antiarrhythmic therapy and clinical benefit
with addition of flecainide [17]. At present, there is no clear indication
of a monogenic role of the R1013Q mutation in the pathogenesis
of ARVD/C. Furthermore, the genetic profile of this patient includes
three gene mutations: two gene mutations in structural proteins, one
of which has been described in patients with ARVC/D, and the third
gene mutation in the RYR2 gene. The relative contributions of each
gene mutation to the phenotype of the disease cannot be ascertained.
The multiple mutations identified in this patient provide a genetic
basis to suggest that combination antiarrhythmic therapy may need
to be considered for refractory ventricular arrhythmias, with potential
beneficial effects of flecainide for R1013Q mutations. However, further
prospective investigations will be needed to guide clinical management
of ARVD/C patients with mutations identified in multiple genes.

![Figure 3: R1013Q mutation location in the cytosolic domain of the RYR2 protein. The black diamonds indicate regional “hot spots” of known missense mutations associated with CPVT (not drawn to scale). CSB/FKB = Calstabin2/FK Binding protein domain. PKA = Protein Kinase A binding domain. CAM = Calmodulin binding domain.](image-url)
References


