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Short communication

Ryanodine receptor 2 (*RYR2*) mutation: A potentially novel neurocardiac calcium channelopathy manifesting as primary generalised epilepsy

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ABSTRACT

Purpose: Ryanodine receptor 2 (*RYR2*) mutation is well-established in the aetiology of an inherited cardiac disorder known as catecholaminergic polymorphic ventricular tachycardia (CPVT). The *RYR2* receptor is expressed in cardiomyocytes, and also in the hippocampus. The *RYR2* mutation has not been reported as a potential cause of adult-onset genetic generalised epilepsy (GGE).

Method: Case report.

Results: A 32-year-old right-handed female presented with three unprovoked generalised seizures over twelve years. Electroencephalogram showed epileptiform activity which coincided with normal electrocardiogram recording. Her brother survived a cardiac arrest in his 20's and was diagnosed with CPVT and found to be heterozygous for a novel mutation in the *RYR2* gene at chromosome 1q43, c.229 G > A p.(Ala77Thr). The patient inherited the same missense variant, predicted to be damaging by numerous in silico analytic tools. This mutation affects the N-terminal domain of the *RYR2* receptor which plays a role in channel activation. However, the patient had repeatedly normal cardiac investigations including normal exercise stress tests.

Conclusion: We propose that the *RYR2* mutation is a potentially novel neurocardiac calcium channelopathy that may manifest with either CPVT or GGE depending on selective involvement of *RYR2* receptors expressed in the heart or in the brain. *RYR2* mutant mice have demonstrated spontaneous EEG-positive seizures independent of cardiac arrhythmia. Whole exome sequencing analyses have identified *RYR2* as a candidate gene in GGE. This case is a reminder for careful assessment of episodes of transient loss of consciousness in an individual with CPVT, so as to not mistake possible neurogenic seizure for cardiogenic syncope, carrying obvious implications for treatment.

1. Introduction

A complex interplay exists between cardiac arrhythmia and epilepsy. One potential association is genetic mutation of a common receptor co-expressed in the heart and in the brain. Ryanodine receptor 2 (*RYR2*) mutation is well-established in the aetiology of an inherited cardiac disorder known as catecholaminergic polymorphic ventricular tachycardia (CPVT). The *RYR2* mutation has not been reported as a potential cause of adult-onset primary generalised epilepsy.

2. Case description

A 32-year-old right-handed female presented with three unprovoked generalised tonic-clonic seizures (GTCS) over twelve years: the first event at age 19 years; second event at age 31 years, and third event at age 32 years. There were no clinical indicators of focal epilepsy, i.e. no aura, automatisms or lateralised posturing. She did not have any inherent risk factors for epilepsy, i.e. normal birth history, normal developmental milestones, no febrile seizures, no history of central nervous system (CNS) infections, no learning disability, and no history of major head trauma. Neurological exam was normal. Electroencephalogram (EEG) showed recurrent paroxysmal and generalised bursts of spike and slow wave activity (Fig. 1). These coincided with normal electrocardiogram (ECG) recording. Magnetic resonance imaging of the brain did not show hippocampal changes or any other potential epileptogenic foci.

Notably, the patient had a remarkable family history that revealed an autosomal dominant pattern of sudden cardiac death; this included survived cardiac arrest in her mother whom, in her mid-30 s, had collapsed suddenly with loss of consciousness while walking; survived cardiac arrest in her younger brother at age 20 years while driving; and sudden cardiac death of one maternal uncle who was found

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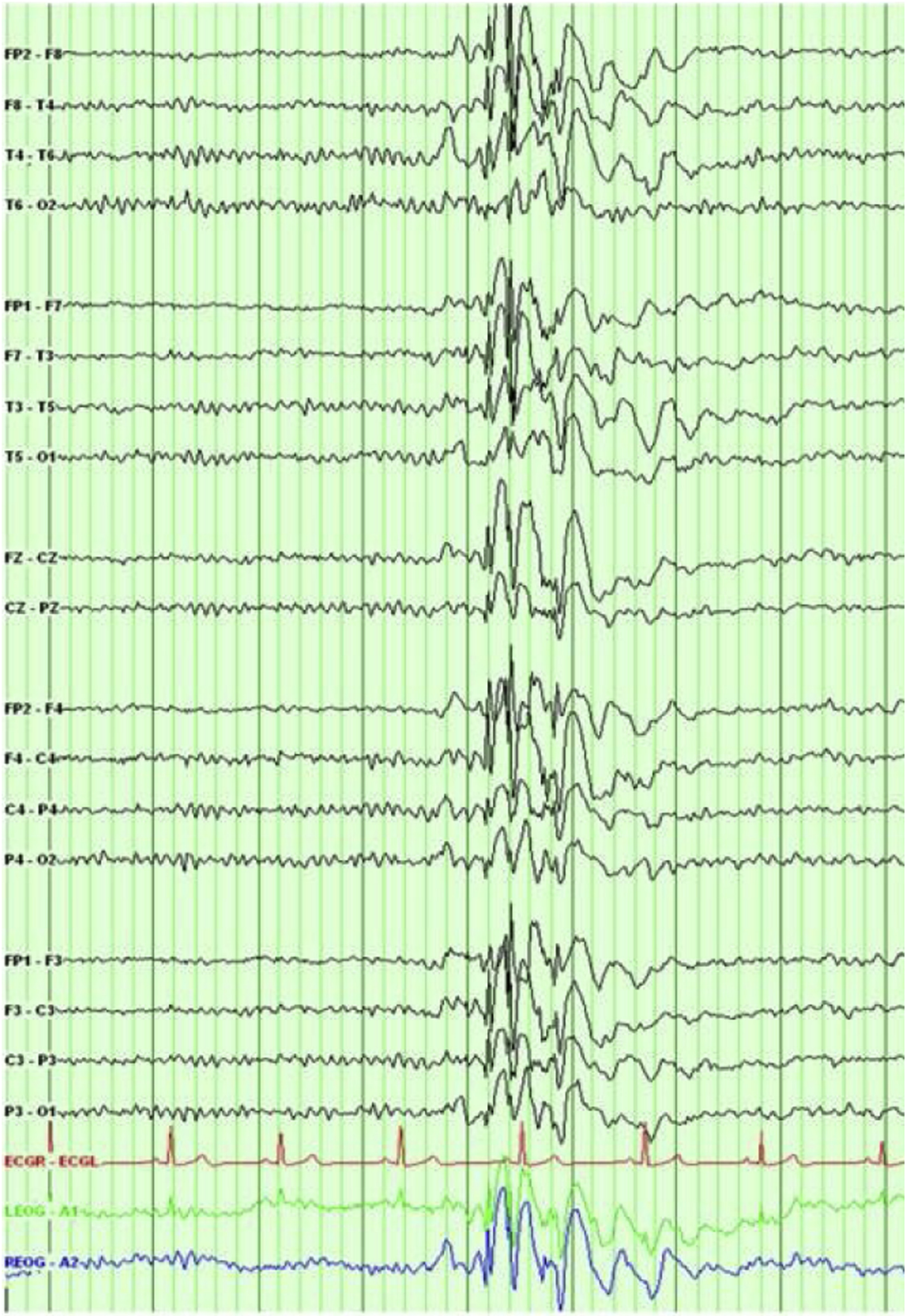

Fig. 1. Electroencephalogram demonstrating paroxysmal generalised outbursts of spike and slow wave activity seen without clinical accompaniment and coinciding with normal electrocardiogram recording.

unconscious and unresponsive in bed at home (Fig. 2a).

Her brother was diagnosed with CPVT and found to be heterozygous for a novel mutation in the *RYR2* gene at chromosome 1q43, c.229 G > A p.(Ala77Thr). The patient herself, at aged 29 years, having suffered only one isolated GTCS at that stage of her life, underwent predictive genetic testing and was found to have inherited the identical *RYR2* mutation, confirmed by Sanger DNA sequencing (Fig. 2b,c). This mutation results in an amino acid substitution in exon 3 representing a region in the N-terminal domain of the *RYR2*-encoded ryanodine receptor (Fig. 2d) [1]. The majority (91%) of in silico

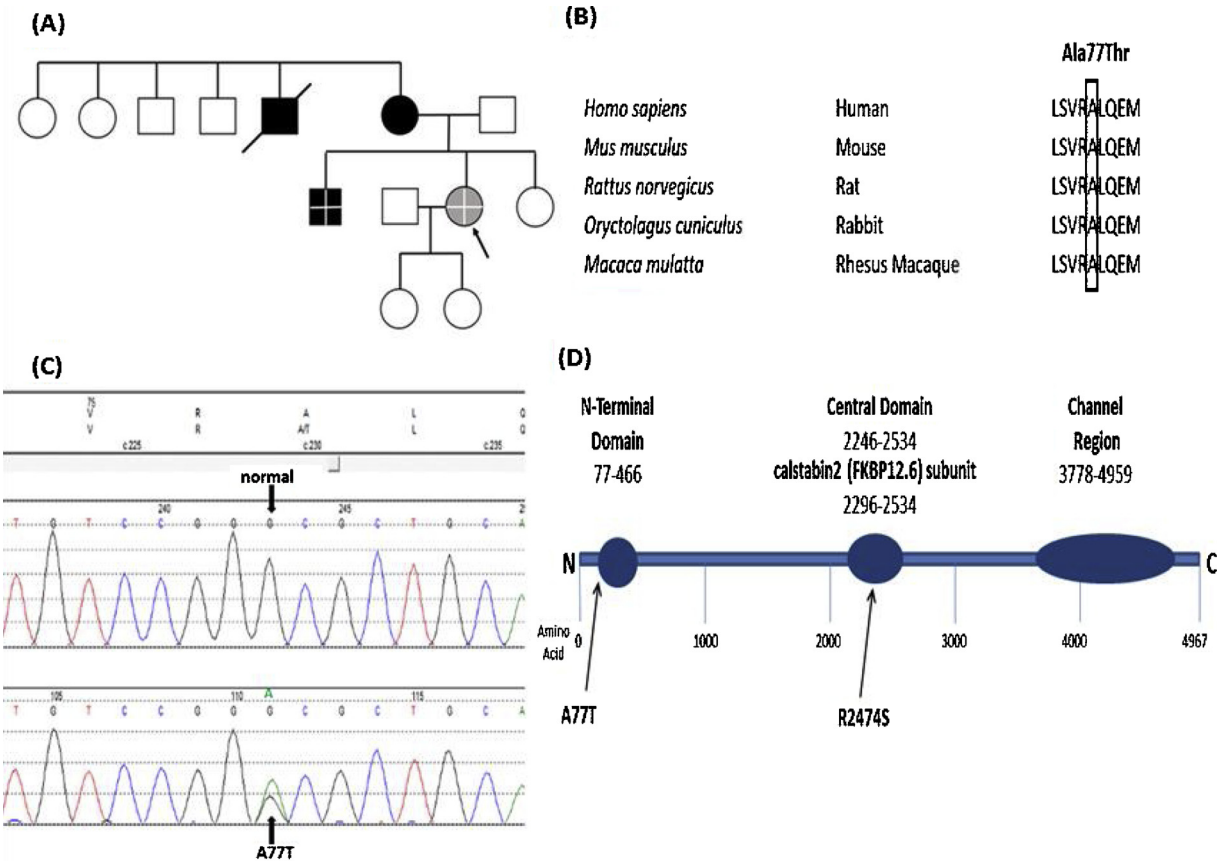

Fig. 2. (A) Family pedigree chart. Black symbols indicate clinically affected, cardiac phenotype. The grey symbol indicates clinically affected, epilepsy phenotype. White symbols indicate clinically unaffected persons. *RYR2* mutation positivity is represented by a cross. Death is represented by a transverse line. The proband is indicated by an arrow. (B) Amino acid conservation at Ala77 across species. (C) Sequence chromatogram of the proband's missense mutation (c.229 G > A, p.Ala77Thr). (D) Topology of the RYR2-encoded ryanodine receptor demonstrating the location of the patient's missense mutation, A77 T, and the location of the R2474S mutation in mice; adapted from Medeiros-Domingo et al, 2009 [1].

analytic tools have predicted this missense variant to be damaging [2]. This variant is absent in the Genome Aggregation Database [2].

Despite being clinically affected, her mother did not have genetic testing performed. Her father, sister and two daughters aged 2.5 years and 1 year respectively were not clinically affected and did not undergo genetic testing for *RYR2* mutation. Importantly, there was no family history of seizures. Interestingly, the patient never described any cardiac symptoms e.g. chest pain, palpitations, dizziness or shortness of breath. She had extensive cardiac investigations performed over the next three years that demonstrated repeatedly normal ECGs, echocardiograms, Holter monitors and exercise stress tests. A loop recorder inserted at some point between the first and second GTCS had not shown any abnormalities up until the present time. She was treated with bisoprolol and levetiracetam.

3. Discussion

This unique case illustrates that the *RYR2* mutation is a potentially novel neurocardiac calcium channelopathy that may manifest with primary generalised epilepsy. The *RYR2* gene encodes the calcium ($Ca2+$) release channel receptor located in the sarcoplasmic reticulum of cardiomyocytes which has an important role in cardiac excitation-contraction coupling [3,4]. Mutations of the *RYR2* gene cause CPVT, an autosomal dominant, young onset, highly malignant cardiac arrhythmogenic disorder characterised by exercise-induced syncope, survived cardiac arrest or sudden cardiac death [3,4].

The *RYR2* receptor is also expressed in the hippocampus and neocortex [3]. As described above, the *RYR2* missense variant in our patient affects the N-terminal domain of the ryanodine receptor. Notably, the N-terminal domain represents a major binding site for the regulatory calstabin2 (FKBP12.6) subunit involved with channel activation [3,5–7]. Mice heterozygous for the *RYR2*-R2474S mutation in exon 49 representing the calstabin2 (FKBP12.6) subunit (Fig. 2c) have demonstrated spontaneous EEG-positive generalised seizures independent of cardiac arrhythmia [3]. Furthermore, other *RYR2* mutant mice have demonstrated spreading depolarisation across the neocortex and brainstem dorsal medulla autonomic microcircuits [8]. Recent whole exome sequencing analyses have identified *RYR2* as a candidate gene in genetic generalised epilepsy and early infantile epileptic encephalopathy [9]. Notably, an 8-year-old female victim of sudden unexpected death in epilepsy (SUDEP) who demonstrated EEG-positive clinical seizures without any cardiac manifestations pre-mortem was eventually found to be *RYR2* mutation-positive post-mortem [10].

The occurrence of primary generalised epilepsy and *RYR2* mutation in our patient may be coincidental. However, one large study of 54 *RYR2* mutation carriers within 12 families revealed that half of the probands but none of the other carriers had presented with presumed neurogenic seizures that were subsequently felt to represent episodes of convulsive syncope instead after exercise ECG demonstrated features suggestive of CPVT [4]. Misdiagnosis between syncope and seizure disorder is not uncommon [4]. One possible reason for the rarity of seizure occurrence in this well-established cardiac arrhythmogenic disorder is enhancement of membrane after-hyperpolarisation in excitatory neurons which acts as a "brake" for aberrant cortical discharges.[8] Furthermore, ion channel gene mutations responsible for cardiac channelopathies such as hereditary long QT syndromes (i.e.

KCNQ1, KCNH2 and SCN5A) have been reported in patients with a neurogenic seizure phenotype and SUDEP; these ion channels have demonstrated co-expression in the heart and in the brain [11]. Seizure generation in our *RYR2* mutation-positive patient may be secondary to an initial undetected cardiac arrhythmogenic event leading to apnoea and cerebral anoxia; however this phenomenon is rare and subject to controversy.[12] Meanwhile, ictal and post-ictal cardiac arrhythmias and autonomic dysfunction are well-described [12].

Importantly, this case serves to improve our routine clinical practice in a number of ways. It highlights the potential relevance of a family history of CPVT in a patient presenting with a seizure. It is a reminder for careful assessment of events involving transient loss of consciousness in an individual with CPVT, so as to not mistake possible neurogenic seizure for convulsive or cardiogenic syncope, carrying obvious implications for treatment. Patients presenting with a first seizure should have a baseline ECG and detailed history taken exploring possible cardiac features. Notably, the decision to treat our patient with levetiracetam was based on evidence that levetiracetam reduces epileptiform activity by modulating intracellular calcium release. Importantly, antiepileptic drugs (AEDs) with sodium blocking properties e.g. carbamazepine, phenytoin and lacosamide should probably be avoided in *RYR2* mutation-positive patients with epilepsy, as they are known to trigger cardiac arrhythmias [12]. Furthermore, such patients should receive specialised counselling with regard to risk of SUDEP [8,11] and importance of maximising seizure freedom with avoidance of seizure triggers and adherence to AEDs.

In conclusion, we report the first clearly defined case of human adult-onset primary generalised epilepsy in an *RYR2* mutation carrier without concomitant cardiac manifestations typical of CPVT. It is biologically plausible that *RYR2* mutations could cause epilepsy in humans. We propose that the *RYR2* gene mutation is a potentially novel neurocardiac calcium channelopathy that may manifest with either CPVT or primary generalised epilepsy depending on selective involvement of *RYR2* receptors expressed either in the heart or in the brain.

Declaration of interests

None

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