Provocation Testing and Therapeutic Response in a Newly Described Channelopathy: RyR2 Calcium Release Deficiency Syndrome

Julian O.M. Ormerod, MD, PhD*; Elizabeth Ormondroyd, PhD*; Yanhui Li, PhD*; John Taylor, PhD; Jinhong Wei, PhD; Wenting Guo, PhD; Ruifu Wang, PhD; Caroline N.S. Sarton, MBiochem; Karen McGuire, PhD; Helene M.P. Dreau, PhD; Jenny C. Taylor, PhD; Matthew R. Ginks, MD, PhD; Kim Rajappan, MD, PhD; S.R. Wayne Chen, PhD; Hugh Watkins, MD, PhD

BACKGROUND: A novel familial arrhythmia syndrome, cardiac ryanodine receptor (RyR2) calcium release deficiency syndrome (CRDS), has recently been described. We evaluated a large and well characterized family to assess provocation testing, risk factor stratification and response to therapy in CRDS.

METHODS: We present a family with multiple unheralded sudden cardiac deaths and aborted cardiac arrests, primarily in children and young adults, with no clear phenotype on standard clinical testing.

RESULTS: Genetic analysis, including whole genome sequencing, firmly established that a missense mutation in RYR2, Ala4142Thr, was the underlying cause of disease in the family. Functional study of the variant in a cell model showed RyR2 loss-of-function, indicating that the family was affected by CRDS. EPS (Electrophysiological Study) was undertaken in 9 subjects known to carry the mutation, including a survivor of aborted sudden cardiac death, and the effects of flecainide alone and in combination with metoprolol were tested. There was a clear gradation in inducibility of nonsustained and sustained ventricular arrhythmia between subjects at EPS, with the survivor of aborted sudden cardiac death being the most inducible subject. Administration of flecainide substantially reduced arrhythmia inducibility in this subject and abolished arrhythmia in all others. Finally, the effects of additional metoprolol were tested; it increased inducibility in 4/9 subjects.

CONCLUSIONS: The Ala4142Thr mutation of RYR2 causes the novel heritable arrhythmia syndrome CRDS, which is characterized by familial sudden death in the absence of prior symptoms or a recognizable phenotype on ambulatory monitoring or exercise stress testing. We increase the experience of a specific EPS protocol in human subjects and show that it is helpful in establishing the clinical status of gene carriers, with potential utility for risk stratification. Our data provide evidence that flecainide is protective in human subjects with CRDS, consistent with the effect previously shown in a mouse model.

Key Words: arrhythmias calcium phenotype ryanodine receptor young adult

Inherited arrhythmia syndromes are an important cause of excess mortality in young people. Survivors of cardiac arrest are carefully phenotyped to diagnose a channelopathy or, conversely, diagnose idiopathic ventricular fibrillation (VF) in which familial recurrence is rare. Gain-of-function cardiac ryanodine receptor (RyR2) mutations cause catecholaminergic polymorphic ventricular tachycardia (CPVT), which is characterized...
by bidirectional/polymorphic VT on exercise or adren- 
aline challenge, recurrent syncope, and sudden cardiac 
death (SCD).3–6 More recently, putative loss-of-function 
RyR2 mutations have been shown to cause ventricular 
arrhythmia (VA) and SCD, often without typical exer-
tional features but sometimes with structural changes or 
bradyarrhythmia7–10; this has been termed RyR2 calcium 
release deficiency syndrome (CRDS).11

Herein, we present our experience of an extended 
family with multiple individuals suffering unprovoked SCD 
or aborted (a)SCD with no prior symptoms and no overt 
phenotype on standard clinical testing. We present genetic 
and cellular characterization of the causal variant together 
with clinical phenotyping, electrophysiological studies and 
drug challenges. Because of the family’s large size, with 
many mutation carriers including several obligate carri-
ers who had not had clinical events or overt phenotypes, 
this analysis has allowed us to address approaches to 
diagnosis, risk stratification, and assessment of treatment 
response in this important new disorder.

METHODS

Detailed methods are available in the Supplemental Material. 
The authors declare that all supporting data are available within 
the article and its Supplemental Material. The human studies 
were performed under protocols approved by the research eth-
ics boards of the participating institutions or as part of planned 
clinical care. All living human study participants provided 
informed consent. Patients consented to data sharing under 
REC approval 09/H0606/108 and WGS under REC approval 
13/WM/0466.

RESULTS

Initial Clinical Findings

The proband (Figure 1; IV:8) suffered aSCD at rest 
while on holiday at the age of 22. There were no obvious 
provoking factors and he had been asymptomatic before 
the episode. The circumstances of his aSCD and the 
lack of any abnormality on exercise stress testing argued 
against a diagnosis of CPVT. Twelve lead ECG (Fig-
ure S1) was normal and negative ajmaline challenge 
excluded Brugada Syndrome. He subsequently had a 
进一步 episode of sustained VA at rest, successfully 
 treated by his implantable cardioverter-defibrillator (ICD) 
(Figure 2D).

The proband’s mother (III:6) suffered a SCD while 
watching television at the age of 24. Postmortem exami-
nation showed idiopathic fibrosis but no evidence of 
cardiomyopathy or myocardial infarction. The proband’s 
great uncle (II:7) died suddenly at the age of 45 after 
jumping from a boat into the sea. The proband’s great 
aunt (II:2) died suddenly at rest at the age of 12.

Cascade clinical testing, including echocardiography, 
drug challenge, ambulatory monitoring, and exercise test-
ing, was continued in the extended family but was made 
challenging by the lack of a consistent clinical phenotype, 
apart from unheralded SCD. A further case of aSCD came to 
light in a distant relative (IV:1). This third cousin 
had aSCD at rest with no provoking factors at age 19. 
He had no prior symptoms and there was no evidence of 
channelopathy or cardiomyopathy on clinical testing.

Results from standard clinical testing are summarized 
in Table S1 and examples given in Figure 2. Taken as a 
whole, there was strong evidence of a familial arrhythmia 
syndrome causing sudden death in young people. There 
were also multiple examples of clinically unaffected oblig-
ate carriers with a normal lifespan. Complex ectopy and 
nonsustained VT (NSVT) were seen in several individu-
als, but these episodes were rare and usually only appar-
ent on extended (>5 days) ambulatory monitoring. Where 
NSVT was apparent during exercise testing this was in 
early exercise or recovery, in contrast to the arrhythmia 
seen at peak exercise in CPVT. No bidirectional VT was 
recorded in any test. Complex ectopy and NSVT can be 
seen in otherwise normal individuals and are not in them-
seles diagnostic of disease. In summary, the results of 
clinical testing were not consistent with any known famil-
ial arrhythmia syndrome; in isolation, the affected indi-
viduals would have been labeled as having idiopathic VF.

Genetic Analysis

Genetic testing in the proband revealed a novel, rare mis-
sensevariantin RYR2 NM_001035.2:c.12424G>A, 
p.(Ala4142Thr) not recorded in gnomAD or other popu-
lation databases, but the significance of this result was 
initially uncertain. Approximately 3% of the normal popu-
lation carry a rare but nonpathogenic variant in RYR2.12 
However, the same variant was present in IV:1. The 
probability of the 2 individuals carrying the variant by 
chance was 0.39%, reflecting segregation over 8 meio-

s. Whole genome testing was undertaken to exclude

Nonstandard Abbreviations and Acronyms

| Abbreviation | Description |
|--------------|-------------|
| CPVT | catecholaminergic polymorphic ventricular tachycardia |
| CRDS | calcium release deficiency syndrome |
| EPS | Electrophysiological Study |
| LBLPS | long burst long pause short-coupled |
| NSVT | nonsustained ventricular tachycardia |
| SCD | sudden cardiac death |
| SOICR | store-over-load induced Ca2+ release |
| VA | ventricular arrhythmia |
| VF | ventricular fibrillation |
| VT | ventricular tachycardia |
| WT | wild type |
the possibility of a segregating variant in cis or another plausible shared variant in a channelopathy-related gene elsewhere in the genome. Only the RYR2 A4142T variant fulfilled criteria for reporting and no other plausible variant was identified in the genome of either patient.

**The RyR2-A4142T Mutation Suppresses Caffeine-Induced Ca\(^{2+}\) Release in HEK293 Cells**

The RyR2-A4142T mutation is located in the U-motif of the central domain that is critical for channel gating\(^ {13}\) (Figure 3). To determine the functional impact of the RyR2-A4142T mutation, we assessed caffeine-induced intracellular Ca\(^{2+}\) release. As shown in Figure 4, in HEK293 cells expressing RyR2-wild type (WT), increasing caffeine concentration progressively increased the level of Ca\(^{2+}\) release (until there was depletion of intracellular Ca\(^{2+}\) stores; Figure 4A). The caffeine response of HEK293 cells expressing comparable levels of the novel RyR2-A4142T mutation (Figure S2) was shifted to the right (Figure 4A and 4B) with an increased EC\(_{50}\) value (Figure 4C) compared with that of WT cells. Thus, the RyR2-A4142T mutation significantly suppresses the caffeine activation of RyR2.

**The RyR2-A4142T Mutation Suppresses Store-Overload Induced Ca\(^{2+}\) Release in HEK293 Cells**

A hallmark of CPVT-causing RyR2 mutations is an enhanced propensity for store-overload induced Ca\(^{2+}\) release (SOICR)\(^ {5,14,15}\). To assess the impact of RyR2-A4142T on SOICR, we monitored spontaneous Ca\(^{2+}\) oscillations in HEK293 cells expressing RyR2 WT and the A4142T mutant. We perfused the cells with elevating extracellular Ca\(^{2+}\) (0–2.0 mmol/L) to induce SOICR and measured the SOICR activity using a fluorescence Ca\(^{2+}\) indicator, fura-2 AM, and single-cell Ca\(^{2+}\) imaging as described previously\(^ {5,15}\). As shown in Figure 4D through 4F, the RyR2-A4142T mutation suppressed spontaneous Ca\(^{2+}\) oscillations (Figure 4D and 4E) and markedly reduced the fraction of cells displaying Ca\(^{2+}\) oscillations (Figure 4F) compared with RyR2-WT.

**The RyR2-A4142T Mutation Increases the Activation and Termination Thresholds for Spontaneous Ca\(^{2+}\) Release in HEK293 Cells**

To investigate how the RyR2-A4142T mutation suppresses the propensity for SOICR, we determined the impact of the mutation on the activation and termination thresholds for SOICR. To measure these thresholds, we promoted spontaneous endoplasmic reticulum (ER) luminal Ca\(^{2+}\) oscillations in HEK293 cells expressing RyR2 WT and the A4142T mutant by perfusing the cells with 1 mmol/L caffeine and increasing concentrations (from 0 to 2 mmol/L) of extracellular Ca\(^{2+}\). Note that elevating extracellular Ca\(^{2+}\) alone (without 1 mmol/L caffeine) was insufficient to induce Ca\(^{2+}\) oscillations in the RyR2-A4142T mutant expressing cells. We used single-cell Ca\(^{2+}\) imaging to monitor the ER luminal Ca\(^{2+}\) dynamics in HEK293 cells using the D1ER-based FRET imaging\(^ {16,17}\). As shown in Figure S3, HEK293 cells expressing RyR2 WT displayed spontaneous ER Ca\(^{2+}\) oscillations with a threshold level
(FSOICR; ≈70%) at which SOICR occurs when the ER luminal Ca\(^{2+}\) content increases, and another threshold level (Fterm; ≈37%) at which SOICR terminates when the ER luminal Ca\(^{2+}\) content decreases. HEK293 cells expressing the RyR2-A4142T mutation significantly increased the SOICR activation threshold and termination threshold (Figure S3B through S3D). As a result, the fractional Ca\(^{2+}\) release (activation threshold−termination threshold) during SOICR was also significantly increased in these mutant expressing cells compared with that of WT cells (Figure S3E). On the other hand, the A4142T mutation had no significant impact on the store capacity (Fmax−Fmin; Figure S3F). Thus, the RyR2-A4142T mutation increases both the SOICR activation and termination thresholds.

Electrophysiological Studies

The long burst, long pause and short-coupled (LBLPS) EPS (electrophysiological study) protocol (Figure 5A, i) has been shown to reliably induce VA in a mouse model of CRDS and in 2 human subjects carrying CRDS mutations but did not induce VA in CPVT model or WT mice.\(^{11}\) Evidence from the CRDS mouse model suggested flecainide might be protective, but this has not been studied in human subjects. We applied the LBLPS protocol to 9 individuals with the A4142T mutation and found a gradation in inducibility between subjects, which correlated with the frequency and duration seen in ambulatory monitoring and exercise testing. We proceeded to test the response to flecainide, and then to the combination of flecainide with metoprolol, revealing a clear effect on arrhythmia inducibility.

We performed diagnostic single wire LBLPS EPS in 9 individuals: III:1, IV:1, IV:2, IV:11, IV:12, IV:9, III:8, III:9, and II:5 (Figure 1). IV:1 was a survivor of aborted SCD. We performed 3 LBLPS studies: baseline, flecainide, flecainide/metoprolol combination. Results are summarized in the Table and example traces are shown in Figure 5. In summary, monomorphic NSVT or sustained VA (monomorphic VT degenerating into VF, or polymorphic VT/torsades de pointes) requiring cardioversion was inducible.
in 7/9 subjects at baseline. No bidirectional VT was seen in any individual. Duration of monomorphic NSVT ranged from 3 beats maximum in III:8 (Figure 5A, ii) to 10 beats maximum in IV:9 (Figure 5A, iii) and III:1. Sustained VA requiring cardioversion was induced in II:5, IV:1, and IV:2. IV:1 additionally had very frequent prolonged episodes of monomorphic NSVT throughout the baseline study, as well as 2 episodes of self-terminating torsades de pointes. Pleomorphic VT began early in the drive train and rapidly degenerated into polymorphic VT/VF in II:5 (Figure 5B, i). Polymorphic VT/torsades de pointes began after a short period of fast monomorphic VT in IV:1 (Figure 5B, ii) and immediately after the short-coupled extrasystoles in IV:2 (Figure 5B, iii). Following flecainide administration, a maximum of 15 beats monomorphic NSVT (but no sustained VA) was inducible in IV:1 (Figure 5C, i) but overall NSVT episodes were shorter and substantially less frequent. No arrhythmia was inducible in any other individual after flecainide (example trace Figure 5C, ii). NSVT was inducible following subsequent metoprolol infusion in IV:1, III:8, IV:9, and IV:11 but not in other individuals.

**DISCUSSION**

The situation at presentation in this family was particularly challenging. There were multiple young adults and children suffering SCD/aSCD, with no prior symptoms and no clear phenotype to guide treatment. In contrast to reports of RYR2 variants associated with atypical phenotypes which frequently remain variants of uncertain significance, in this family whole genome sequencing in 2 distant affected relatives confirmed the A4142T variant as the highly likely cause. In vitro cell model data show that the A4142T variant causes a loss-of-function of RyR2 in a similar manner to recently described cases of the novel channelopathy CRDS. The situation at presentation in this family was particularly challenging. There were multiple young adults and children suffering SCD/aSCD, with no prior symptoms and no clear phenotype to guide treatment. In contrast to reports of RYR2 variants associated with atypical phenotypes which frequently remain variants of uncertain significance, in this family whole genome sequencing in 2 distant affected relatives confirmed the A4142T variant as the highly likely cause. In vitro cell model data show that the A4142T variant causes a loss-of-function of RyR2 in a similar manner to recently described cases of the novel channelopathy CRDS.11

**CRDS Is Challenging to Diagnose Using Standard Clinical Assessments**

SCD is relatively common in our family but multiple gene carriers appear unaffected and have not suffered SCD, syncope, or other intrusive symptoms and appear to live

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**Figure 3. Location of the A4142T mutation in the cardiac ryanodine receptor (RyR2).**

A. A schematic diagram of the linear sequence of RyR2. Major structural domains of RyR2 are depicted as solid blue boxes. The orange boxes indicate 4 disease-associated mutation clusters (mutation hotspots) in RyR2. The RyR2-A4142T mutation is shown underneath the corresponding domain. B. Location of the RyR2-A4142T mutation in the central domain (critical for channel gating) in the 3-dimensional (3D) structure of RyR2 (PDB: 6JI0). The cytosolic Ca²⁺, ATP, and caffeine binding sites and the channel pore-forming domain are also indicated.
a normal lifespan. This means that the familial nature of this condition might not be obvious to the clinician or indeed the patient and their immediate relatives. A high level of suspicion and a detailed, extensive family history are required. The phenotype of CRDS is substantially different from CPVT. In our family, complex ectopy and NSVT (where present) tended to occur at rest, in early exercise or in recovery, rather than at peak exercise, and were never marked. Arrhythmia in general was seen far less frequently than is typical in clinically apparent CPVT, requiring prolonged (≥5 days) ambulatory monitoring to detect it in several cases. Complex ectopy and NSVT can be seen in otherwise normal older adults (although less commonly in children and young adults), so these subtle findings on ambulatory monitoring and exercise testing are difficult to distinguish from normality. The diagnostic value of provocation testing using the LBLPS protocol, revealing the phenotype in otherwise asymptomatic gene carriers is, therefore, considerable. When assessed with this diagnostic test, the penetrance of this disorder is seen to be high (Figure 6).

The RyR2-A4142T Mutation Causes Distinctive Changes in Channel Function Which Match the Clinical Natural History

Our in vitro studies show that the RyR2-A4142T mutation decreases channel sensitivity to caffeine and raises the threshold of activation for SOICR. As a result, the mutation is likely to diminish the responsiveness to elevated SR Ca²⁺ store induced by β-adrenergic stimulation. However, the lack of SOICR could lead to increased SR Ca²⁺ content and abnormally large depolarization induced Ca²⁺ transients especially after a long burst and a long pause, which can lead to early afterdepolarizations. These results may relate to the clinical observation that arrhythmia episodes appear uncommon in CRDS and are not associated with exercise or stress, but arrhythmia appears poorly tolerated when it occurs. It is notable that no family member suffering SCD/aSCD had a reported prior history of syncope or near syncope. This is in contrast to CPVT, where syncope is common.

Risk Stratification in CRDS

Risk stratification balances the risk of fatal VA against the risk of ICD complications, which can themselves be fatal and are substantially more common in younger

Figure 4 Continued. Ca²⁺ (0–2 mmol/L) to induce SOICR. Fura-2 ratios of representative RyR2 WT and A4142T mutant cells were recorded using single-cell Ca²⁺ imaging. F, The percentages of RyR2 WT and A4142T cells that display Ca²⁺ oscillations at various extracellular Ca²⁺ concentrations. Data shown are mean±SEM (n=5 separate experiments; *P<0.05 vs WT). RyR2 WT data were taken from a previous work where the RyR2-A4142T mutant was an unpublished part of the experimental study.

**Figure 4.** The RyR2-A4142T mutation suppresses caffeine-induced Ca²⁺ release and store-overload induced Ca²⁺ release (SOICR) in HEK293 cells. A, HEK293 cells were transfected with RyR2 wild type (WT; 1) and the A4142T mutant (2). Fluorescence intensity of the fluo-3-loaded transfected cells was monitored continuously before and after each caffeine addition. The numbers (under the traces) indicate caffeine concentrations (mmol/L). Traces shown are from representative experiments. B, Cumulative caffeine concentration–Ca²⁺ release relationships in HEK293 cells transfected with RyR2 WT and A4142T. C, The apparent EC₅₀ (mmol/L) values of caffeine-induced Ca²⁺ releases in HEK293 cells transfected with RyR2 WT or A4142T. Stable, inducible HEK293 cells expressing RyR2 WT (D) or the A4142T mutant (E) were loaded with 5 μmol/L Fura-2 AM in Krebs-Ringer-Hepes (KRH) buffer. The cells were then perfused continuously with KRH buffer containing increasing levels of extracellular Ca²⁺.
people with a longer predicted exposure to device therapy. These challenges were compounded in the current family by the lack of a definitively pathological observed phenotype on standard clinical testing, the absence of preceding symptoms and no proven therapeutic alternative to an ICD. In this small group of patients, EPS results appeared to correlate with the clinical phenotype: most clearly with cardiac arrest status, but also with the frequency and complexity of ectopy and NSVT seen on ambulatory monitoring and on exercise testing. For example, it was not possible to induce arrhythmia at baseline in IV:11 and III:9, and there was no arrhythmia seen in either patient on exercise or ambulatory monitoring. III:8 was asymptomatic and showed only a small degree of complex ectopy on ambulatory monitoring (Figure 2A) and only short bursts of NSVT were inducible at EPS (Figure 5A, ii). In contrast, II:5, who had a history of syncope with injury and showed NSVT in early exercise and recovery (Figure 2C), displayed sustained VA requiring cardioversion at EPS caused by rapid pacing alone (Figure 5B, i). By far the highest frequency of inducible NSVT (and an episode of sustained VA requiring cardioversion, Figure 5B, ii) was seen in IV:1 who was a survivor of cardiac arrest. Flecainide reduced the frequency and duration of NSVT but did not entirely abolish it in this individual (Figure 5C, i). This suggests that this specific EPS protocol, as well as being diagnostically useful in CRDS, might also shed light on risk stratification to determine

![Figure 5. Response to the long burst, long pause and short-coupled (LBLPS) EPS (Electrophysiological Study) protocol in patients with A4142T+−.](image)

**Figure 5.** Response to the long burst, long pause and short-coupled (LBLPS) EPS (Electrophysiological Study) protocol in patients with A4142T+−.

A, i, Graphical representation of the LBLPS protocol; (A, ii) example of 3 beats nonsustained ventricular tachycardia (NSVT) induced at EPS in III:8 (15 beat drive train cycle length 430 ms, S1 720 ms, and S2 200 ms); (A, iii) and 10 beats NSVT induced at EPS in IV:9 (drive train cycle length 370 ms, S1 620 ms, and S2 300 ms); (B, i) Pleomorphic VT degenerating into ventricular fibrillation (VF) following 7 beats of 300 ms drive train in II:5 (B, ii) sustained polymorphic VT starting immediately after the short-coupled extrasystoles in IV:1 (drive train cycle length 370 ms, S1 800 ms, and S2 300 ms); (B, iii) sustained polymorphic VT starting immediately after the short-coupled extrasystoles in IV:2 (drive train cycle length 300 ms, S1 550 ms, and S2 200 ms); (C, i) NSVT was inducible after flecainide in IV:1 (maximum 15 beats at drive train cycle length 300 ms, S1 700 ms, and S2 400 ms); (C, ii) no arrhythmia was inducible following flecainide in any other individual (example normal trace given). S1 indicates first programmed extrasystole; and S2, second programmed extrasystole.

### Table. Summary of Findings in Individuals Who Underwent Electrophysiological Testing

| Subject | Ambulatory | Exercise | Baseline | +Flecainide | +Metoprolol |
|---------|------------|----------|----------|-------------|-------------|
| III:1   | +          | −        | +        | −           | −           |
| IV:1    | −          | −        | +        | +           | +           |
| IV:2    | −          | −        | ++       | −           | −           |
| IV:11   | −          | −        | −        | −           | +           |
| IV:12   | −          | −        | +        | −           | −           |
| III:9   | −          | −        | −        | −           | −           |
| IV:9    | +          | −        | +        | −           | +           |
| III:8   | −          | −        | +        | −           | +           |
| II:5    | +          | +        | ++       | −           | −           |

+ indicates NSVT (3 or more beats, >120 bpm); ++, sustained VA requiring cardioversion; EPS, Electrophysiological Study; and NSVT, nonsustained ventricular tachycardia.
which gene carriers would benefit from ICD implantation. Data from more subjects over a longer follow-up interval are needed before this can be confirmed as a clinically useful strategy. At present we have implanted ICDs in 2 additional individuals in response to sustained VA at EPS and used flecainide in individuals where it appeared beneficial (Figure 6).

**Drug Treatment in CRDS**

The results of clinical electrophysiological testing point to a beneficial effect of flecainide in suppressing inducibility of VA. This suggests that flecainide may be useful in preventing further therapies in those who have suffered repeated ICD shocks and may prevent first episodes of VA in asymptomatic carriers. If successful, this strategy would be preferable to widespread ICD implantation in a young cohort of patients who, despite the relatively high risk of VA and SCD in the family as a whole, may never suffer SCD themselves. Flecainide is widely available and well tolerated and so is an ideal candidate for antiarrhythmic therapy for CRDS. Our data suggest a possible deleterious effect of metoprolol in combination with flecainide, at least in some individuals, but further testing is warranted.

**Limitations**

These data pertain to a single extended family with CRDS due to the RyR2-A4142T mutation. The present study adds to the clinical experience with this novel condition but more data are needed. VAs seen at EPS do not necessarily correlate with those arising spontaneously, although it was striking that the clinical arrhythmia recorded by the ICD of the proband (Figure 2D) was similar to the sustained VA induced in his relative on EPS (Figure 5B, ii) and to that documented in mouse models.\(^1\)  We have not tested the LBLP5 EPS protocol in CPVT patients or in healthy volunteers, but it did not induce VA in WT or CPVT model mice.\(^2\)\(^0\)\(^2\)\(^1\)  Only long-term experience can determine if the beneficial effect seen with flecainide at EPS improves overall outcomes. Further study is needed to establish the effect, deleterious or otherwise, of beta-blockers in combination with flecainide.

**Conclusions**

We have described an extended family with multiple cases of unheralded SCD affecting predominantly young adults. The large size of the family allowed us to confidently ascribe the risk to a loss-of-function variant in RyR2, which is a cause of the novel channelopathy CRDS. Standard clinical testing did not show any recognizable phenotype, reflecting the concealed nature of this disorder, but testing with a specific EPS protocol in several family members showed promise as a diagnostic test and gave evidence of a protective effect of
flecainide. The variable inducibility of VA at EPS correlated with the degree of complex ectopy and NSVT seen in ambulatory monitoring and exercise testing, suggesting that this EPS protocol might additionally be useful for risk stratification in this newly described channelopathy. The prevalence of CRDS is unknown and the diagnosis is easily missed. It may explain a proportion of patients diagnosed with idiopathic VF, wherever there is a family history of SCD, even in quite distant relatives.

**ARTICLE INFORMATION**

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**Affiliations**

Division of Cardiovascular Medicine, Radcliffe Department of Medicine (J.O.M.O., E.O., H.W.), Molecular Diagnostic Centre, Department of Oncology (H.M.P.D.), and Oxford Biomedical Research Centre and Wellcome Centre for Human Genetics (J.C.T., H.W.), University of Oxford, United Kingdom. Cardiac Rhythm Management Service, Oxford Heart Centre, John Radcliffe Hospital, United Kingdom (J.O.M.O., M.R.G., K.R.). Department of Physiology and Pharmacology, The Libin Cardiovascular Institute, University of Calgary, AB, Canada (Y.L., J.W., G.W., R.W., S.R.W.C.). Department of Internal Medicine, Institute of Hypertension, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (Y.L.). Oxford Medical Genetics Laboratories, Cardiac Service, Oxford University Hospitals NHS Trust, The Churchill Hospital, United Kingdom (J.T., C.N.S.S., K.M., J.C.T.).

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**Disclosures**

None.

**Supplemental Material**

Supplemental Methods

Table S1

Figures S1–S3

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